Global, regional, and national prevalence of diabetes mellitus in patients with pulmonary tuberculosis: a systematic review and meta-analysis

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Abstract

Background. The concept that people with pulmonary tuberculosis are at risk of developing diabetes mellitus has been raised. However, the prevalence of diabetes mellitus in patients with pulmonary tuberculosis have not been well established. We aim to estimate the global, regional, and national prevalence of diabetes mellitus in population with pulmonary tuberculosis.

Methods. In this systematic review and meta-analysis, we assessed observational studies of diabetes mellitus in people with pulmonary tuberculosis, using PubMed and Embase electronic bibliographic databases in English language, to identify articles published until August 31, 2018. We included original research studies published in a peer-reviewed journal and reported the prevalence of diabetes mellitus or had enough data to compute these estimates. Studies were excluded if they did not provide primary data or were case studies and reviews. Independent extraction of articles and collected detailed information by 2 authors using predefined questionnaire, including study quality indicators. The country-specific random-effects meta-analyses for countries with two or more available studies and a fractional response regression model to predict individual studies prevalence of diabetes mellitus in patients with pulmonary tuberculosis for countries with one or no study. The study is registered with PROSPERO, registration number CRD42018101989.

Results. We identified 18042 studies, and 127 were retained for data extraction across 46 countries. The global prevalence of diabetes mellitus in patients with pulmonary tuberculosis were estimated to be 12.07% (95%CI: 10.43-14.85). The prevalence of diabetes mellitus in patients with pulmonary tuberculosis was 13.38% (95%CI: 11.16-16.05) in region of Americas, 13.34% (95%CI: 12.82-14.61) in European region, 12.68% (95%CI: 9.15-16.37) in South-East Asia, 12.56% (95%CI: 11.79-22.70) in Western Pacific region, 10.95% (95%CI: 9.04-17.83) in Eastern Mediterranean region and 7.54% (95%CI: 6.51-8.77)in African region. The country
with the highest estimated prevalence of pulmonary tuberculosis combined diabetes mellitus were Mauritius (39.65%, 95%CI: 4.22-90.74). Conclusion. Our findings suggest that pulmonary tuberculosis combined diabetes mellitus is still prevalent. As such, diabetes mellitus deserves more attention from PTB health-care providers, researchers, policy makers, and stakeholders for improved detection, overall proper management, and efficient control of diabetes mellitus in people with pulmonary tuberculosis.

Background

Both TB and DM are major global public health problem. Despite the laudable progress policies and medical cares in control of TB, it remains a huge global health threat [1]. Approximately 10 million people develop TB disease in 2017, and TB caused an estimated 1.3 million deaths [2]. Meanwhile, DM, a non-communicable disease, has been an increasing epidemic in recent decades [3]. As of 2015, more than 415 million adults have DM, and this number is estimated to increase to 642 million by 2040 [4].

Since the early part of the 20th century, clinicians have observed an association between DM and TB [5-7]. The association between TB and DM has been described as co-epidemic [8]. Data shows that the risk of developing DM in people with TB was three times as in those without, suggesting that the TB epidemic is fueling the DM epidemic [9]. According to another systematic review, DM also have a major effect on TB treatment outcomes [10]. It showed that TB patients with DM had higher risk of failure, relapse, and death combined than those without. Considering the dual burden of those two diseases, World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (The Union) launched a collaborative framework, which emphasizes the need to establish collaborative mechanism between national tuberculosis programs (NTPs) and diabetes organizations and the bi-directional screening of TB and DM [11].

More and more studies had screening patients with TB or PTB for DM in some countries
[12-21], and the global burden of DM among patients with TB have been estimated [22]. However, the global prevalence of DM in patients with PTB, the most common form of TB, has not been fully understood. Therefore, we did the comprehensive epidemiological study to estimate the global, regional, and national prevalence of DM (any type) in patients with PTB, which would help researchers to better understand the global epidemiology condition and estimate the global burden of PTB combined DM for the data are spares and incomplete in many countries. We expected the results to provide the most update information on the rate of DM among PTB patients in nation, region and global.

Methods
We conducted our systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [23]. The full review protocol is available in International prospective register of systematic reviews (PROSPERO), registration number CRD42018101989.

Search strategy and selection criteria
We developed a comprehensive systematic literature search to standardize all screening and identify all studies that have reported the prevalence or the number of DM in patients with PTB in any country. We searched PubMed and Embase to identify all relevant cohort, cross-sectional, and case-control studies published up to August 31, 2018 on the prevalence of DM in patients with PTB, with English language. We included original research studies published in a peer-viewed journal with English. Detailed description of the main keywords for the search strategy is available in Appendix.

Articles were retained if they were primary studies had to be observational studies of people with PTB and reported the prevalence of DM, or have enough data (e.g., number of DM cases and sample size) to compute these estimates. We included case-control studies for PTB as the case group and reported the prevalence or number of DM in the case group.
In our inclusion criteria, we did not considerate the definition of PTB assessment (medical records, microbiologically confirmed or other) and the definition of DM assessment (self-report, medical records or laboratory tests).

We excluded studies in subgroups of participants selected on the basis of the presence of DM; studies that were case series, letters, reviews, commentaries, editorials, or animal reports; and studies without primary data or explicit description of methods. If multiple reports originated from the same dataset, we considered the most comprehensive study that reported the largest sample size. We appraised the quality of each included study using a modified version of a critical appraisal tool for use in systematic reviews addressing questions of prevalence [24].

**Data collection and management**

We designed a customized questionnaire (Appendix, P5) and Epidata database for data extraction. Extracted data included: number of the article which assured by the published chronology, title, Published time, study design, number of PTB, number or prevalence of DM in PTB patients and so on (concrete items in appendix p4). Two authors (MML and ZQH) independently extracted relevant information entering EpiData 3.1 software. Disagreement were resolved by team discussions in articles retained and data extracted. Meanwhile we collected the information of TB incidence, Gross Domestic Product (GDP), Human Development Index (HDI) and Human Capital Index (HCI) from the website of World Bank Open Data [25].

**Data analysis**

Country-specific random-effects meta-analysis method was used to estimate the pooled prevalence of DM in PTB patients for countries with two or more empirical studies. Before doing the meta-analysis, the prevalence of DM in PTB patients reported in each studies were transformed using a double arcsine transformation.
For countries with one or no empirical studies, we predicted the country’s prevalence of DM in PTB patients by using a multilevel fractional response regression modelling. In detail, we generalized a linear model with a binomial family and a logit link to restrict final predictions ranged from zero to one. The following predictor variables were added in the fractional response regression model: no predictor variables (Model 1) study years and Gross Domestic Product (GDP) in the study year or nearest year if GDP was unavailable in the study year (Model 2), and the other model including the variables study years, GDP, Human Development Index (HDI) in the study year or nearest year if GDP was unavailable in the study year and Human Capital Index (HCI) in the year of 2017 (Model 3) to predict the prevalence of PTB combined DM. Data of GDP, HDI and HCI come from the World Bank Open Data website. The standard error for each country estimate was based on the variation between studies included in the meta-analysis.

To estimate prevalence of DM in PTB by the six WHO regions and globally. We calculated a weighted average of the prevalence of DM in PTB weighted by the predicted number of TB patients in each country for the latest available year (2016). To estimate the confidence interval (CI) of these point estimates, we used Monte Carlo method (drew 1000,000 samples per country) to generate the corresponding 1000,000 weighted averages of regions and globally. The normal distribution assumption of averages were used to estimate the CI.

Heterogeneity between studies estimates of the prevalence of DM in PTB patients was assessed using the $I^2$ statistic [26]. We considered an $I^2$ of 25% to 49% as low, 50% to 74% as moderate, and 75% or greater as high heterogeneity [27]. We used Egger’s test to detect publication bias [14]. A $P$ value less than 0.10 on Egger's test was considered indicative of statistically significant publication bias. It was decided a priori that if publication bias were present it would not be adjusted for, since it was assumed that the
prevalence estimates of interest would likely be published even if substantially different from previously reported estimates. All analyses were performed using Stata 15.0 (Stata Corporation, College Station, TX) [28].

Results

Search Results

We initially identified 18042 records in the literature search. After elimination of duplicates, 14993 records remained. We screened the titles and abstracts and excluded 14542 irrelevant records. We conducted full text review of 451 papers, excluding 324 papers for 295 studies lacked relevant data, 24 studies did not meet inclusion criteria (3 case reports, 17 insufficient information, 4 case control studies which considered the TB-DM or PTB-DM as the case, and 39 studies) and 6 duplicate studies. Finally, 127 studies contained 132 estimates from 46 countries were included in the meta-analysis to estimate the prevalence of DM in PTB patients (figure1). The critical appraisal of included studies and a complete reference list of all included studies is available in the appendix (appendix p11 table 3).

Study Characteristics

Data were available for 11 of 15 countries in the African Region; 6 of 12 countries in the Eastern Mediterranean Region; 8 of 9 countries in the European Region; 7 of 30 countries in the Region of Americans; 7 of 30 countries in the South-east Asian Region; and 7 of 36 countries in the Western Pacific Region. There were 17 countries with two or more studies, and the three countries with most studies were China (22), India (20), and Mexico (9). All included articles and it reported the prevalence of DM in PTB patients are shown in the appendix (appendix p6 table2).

Pooled Estimates

The prevalence of DM in PTB patients was estimated for 185 countries (via meta-analysis
for 17 countries [with two or more available empirical studies] and via statistical modelling [prediction] for 168 countries). The prevalence of DM in people with PTB could not be estimated for 8 countries because of missing data for one or more predictor variables. The final model included the following predictor variables: GDP ($\beta=0.001$ [referring to an increase of 100 000 international dollars], 95%CI -0.009 to 0.012), HDI ($\beta=0.235$ [referring to an 10% increase], 95%CI -0.959, 1.428), TB incidence ($\beta=-0.002$ [referring to an 1% increase], 95%CI -0.008 to 0.007) and DM prevalence ($\beta=0.089$ [referring to an 1% increase], 95%CI -0.135, 0.313).

**National Prevalence of DM in patients with PTB**

The five countries with the highest estimated prevalence of DM in patients with PTB were Mauritius (39.65%, 95%CI 4.22-90.74), United Arab Emirates (32.83%, 95%CI 6.17-78.41), Qatar (31.71%, 95%CI 6.33-76.14), Bahrain (31.55%, 95%CI 6.21-76.23), and Mexico (31.32%, 95%CI 26.35-36.53; $I^2=98.5\%$, based on meta-analysis of 9 studies). The five countries with the lowest prevalence of DM in patients with PTB were Niger (3.90%, 95%CI 0.05-78.30), Sierra Leone (4.33%, 95%CI 0.17-54.28), Liberia (4.51%, 95%CI 0.21-51.59), Burkina Faso (4.58%, 95%CI 0.10-72.07) and Mali (4.59%, 95%CI 0.10-71.50). The prevalence of DM in PTB patients, by country, is shown in figure 2 and in the appendix (table 4). The results of the tests of heterogeneity and publication bias for the meta-analysis of prevalence of diabetes mellitus with pulmonary tuberculosis, by country, are shown in the appendix (appendix p18 table 5).

**Global and Regional prevalence of DM in patients with PTB**

The global prevalence of DM in patients with PTB was estimated to be 12.07% (95%CI 17.3-19.8). The highest prevalence of DM in patients with PTB was in Region of Americans (13.38%, 95%CI 11.16-16.05), and the lowest prevalence of DM in patients with PTB was in the African Region (7.54%, 95%CI 6.51-8.77). The prevalence of DM in patients with PTB
were 13.34% (95%CI 12.82-14.61) in the European Region; 12.68% (95%CI 9.15-16.37) in the South-east Asian Region; 12.56% (95%CI 11.79-22.70) in the Western Pacific Region; 10.95% (95%CI 9.04-17.83) in the Eastern Mediterranean Region, The prevalence of DM in patients with PTB by WHO region and global are shown in the table 1.

Discussion

Summary of Findings

Present study was estimated the global, regional, and national prevalence of DM in patients with PTB for the first time. Although the prevalence of PTB appears to be decreasing overall, PTB combined DM is still prevalent in several countries. We found that the global predicted prevalence of DM in patients with PTB was 12.07% (95%CI 10.43-14.85). The distribution of prevalence among the regions was ranged from 7.54% (95%CI: 6.51-8.77, African region) to 13.38% (95%CI: 11.16-16.05, region of the Americas) and the prevalence among the countries was ranged from 3.90% (95%CI: 0.05-78.30) in Niger to 39.65% (95%CI: 4.22-90.74) in Mauritius.

Difference of prevalence

The prevalence of DM in people with PTB was higher in Region of the Americas, European Region, South-East Asia region, Western Pacific Region, than global prevalence, and the African region has the lowest prevalence of PTB combined DM. Some factors may explain why the different regions have different prevalence in our meta-analysis. In Mexico border, communities are burdened by poverty, crowding, low-economic status and illegal immigration, and have higher PTB incidence rate and DM has a growing trend, which caused the highest prevalence of PTB combined DM in Mexico [29], and caused higher prevalence of PTB combined DM in region of American indirectly [30]. The European region has the high prevalence of DM in PTB patients, which can attributed that sound infection disease prevention and system better-resourced health systems made PTB well controlled,
while the rich dietary and multiple lifestyle results in DM prevalent in European [31]. India, has the highest number of TB cases (27%) in the world and very high burden of DM, which bring about the higher prevalence of PTB combined DM in the India even in the South-East Asian region [32]. As we know, TB remains a major public health problem in many middle-income countries such as the Western Pacific Region of China [33,34], at the same time, the prevalence of DM is on the rise in middle-income countries for the changes of dietary patterns and lifestyles with the development of technological and economic [35-37]. These all may be contribute to the higher prevalence of PTB combined DM in Western Pacific Region. The African region has the lowest prevalence could be explained by the lack of some risk factors recognized for the onset of DM, including overweight, aging of population, and hypertension [18]. Meanwhile most of PTB and DM cases were not registered at the local department and majority facilities were still not screening DM in PTB patients partly due to cost, perceived complexities, and lack of the treatment infrastructure for those who screen positive can lead to under-diagnosed the prevalence of DM among patients with PTB in African [38-41].

**Biological Plausibility**

Numerous studies have presented convincing biological evidence in support of the causal relationship between DM and impaired host immunity to TB. In several recent animal models of Mycobacterium tuberculosis (Mtb) have demonstrated that unexpected development of DM, particularly those treated with anti-glycaemic therapy as host-directed therapy for TB [42]. Thus, PTB disease may identify individuals at higher risk of progression to DM. Another possible mechanism by which PTB may increase DM risk is through changes in body composition during and following the illness. Patients with PTB frequently lose a substantial amount of weight before and in early stages of treatment; limited evidence from cohort studies suggests that weight regain during treatment could
increase the proportion of body fat in recovered patients with tuberculosis, hence increasing their future risk of DM [43,44].

**Public Health Suggestion**

Given the high prevalence of PTB combined DM and its adverse outcome, we strongly believed that greater investments are needed to improve. There are some suggestions: for the department of public health, early bi-directional screening DM for PTB patients especially in African region as well as improving collection and monitoring of data for PTB and DM are necessary; for the organization of clinical medicine, developing and implementing clinical guidelines and tools to improve the management of PTB at risk of DM and care of PTB combined DM are also crucial; for the institution of medical research, more researches are needed to understand whether DM caused PTB or whether PTB led to the clinical manifestations of DM on the mechanism, so it can be better predicted and prevented.

**Limitation**

There are several potential limitations to this study. First, we have not included studies published in all language, which could have resulted in a reduction in the number of studies we researched. As we known, high quality studies tend to be published in English and our team does not have anyone who knows other language except for English and Chinese. So we only searched English articles. Second, the inclusion of studies which did not consistently define the diagnosis of PTB and DM because of the different criterions in different countries. However, the diagnosis of PTB and DM in most of countries reference to WHO standards. Third, the predicted prevalence estimates for the 168 countries with either one or no available study might diverge from the actual prevalence because the data from which the values were predicted carry some measurement error, and other relevant explanatory variables might affect the prevalence of DM with PTB and not be
possible to account for. However, taking into consideration the study and that we were limited to the information reported in the included studies, we consider the present model to yield the best estimates. Fourth, as would be expected when pooling estimates across locations, we observed high heterogeneity ($I^2=97.5\%$) in the meta-analysis. However, heterogeneity can be overestimated when summarizing studies with large sample sizes [45]. Finally, it should also be noted that this study was limited to WHO Member States.

**Conclusions**

In conclusion, PTB combined DM is a crucial global health issue, which must be addressed to reduce adverse treatment outcomes and mortality globally and improve quality of patients life. Better recognition, prevention, and management of PTB combined DM to early reach the Sustainable Development Goals. Our findings suggest that early standardized bi-directional screening DM in TB patients and TB in DM patients should implementation as soon as possible. DM controls programs also should consider target patients with PTB for interventions such as active case finding and the treatment of hyperglycemia and, conversely, that efforts to diagnose, detect, and treat PTB may have a beneficial impact on DM control. To better understand the global epidemiology of DM in patients with PTB, the quality and volume of data needs to be strengthened, including standardization in definitions, measurement, monitoring, and reporting. Further research on cause of PTB combined DM and new interventions to prevent and manage the consequence of PTB combined DM (particularly in low and middle-income region) are also need.

**Abbreviations**

PTB, pulmonary tuberculosis; DM, diabetes mellitus; TB, tuberculosis; WHO, World Health Organization; NTPs, National Tuberculosis Programs; PROSPERO, International prospective
register of systematic reviews, GDP, Gross Domestic Product; HDI, Human Development Index; HCl, Human Capital Index; IDF, International Diabetes Federation; CI, confidence interval; Mtb, Mycobacterium tuberculosis

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**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable

**Availability of data and materials**

The dataset supporting the conclusions of this article is included within the article’s appendix file (Appendix file 1).

**Competing interests**

The authors declare that they have no competing interests.

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**Author contributions**

CL, TC, and MML conceived the study and developed the protocol. MML and ZQH did the literature search, selected the studies, extracted the relevant information, and synthesized the data. CL did the statistical analysis. MML, CL, and TC wrote the first draft of the paper. MML, CL, TC, ZQH, ZQL, YJK, HY, and DLW critically revised successive drafts
of the paper and approved its final version. LC is the guarantor of the study.

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**Tables**

Table 1. Global prevalence (%) of DM in patients with PTB, by country and WHO region

| WHO Region                  | Prevalence (%) | 95% confidence interval |
|-----------------------------|----------------|-------------------------|
|                             |                | Lower      | Upper      |
| African Region              | 7.54           | 6.51       | 8.77       |
| Eastern Mediterranean Region| 10.95          | 9.04       | 17.83      |
| European Region             | 13.34          | 12.82      | 14.61      |
| Region of the Americas      | 13.38          | 11.16      | 16.05      |
| South-East Asia region      | 12.68          | 9.15       | 16.37      |
| Western Pacific Region      | 12.56          | 11.79      | 22.70      |
| Globally                    | 12.07          | 10.43      | 14.85      |

WHO: world health organization

**Figures**
Figure 1

Flow chart of literature search for studies on the prevalence of DM in patients with PTB
Figure 2

Global prevalence of PTB combined DM

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

Appendix.doc