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Meta-Analysis: The Association Between HIV Infection and Extrapulmonary Tuberculosis

Cho Naing · Joon Wah Mak · Mala Maung · Shew Fung Wong · Ani Izzuani Binti Mohd Kassim

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Abstract
Background Extrapulmonary tuberculosis has been an AIDS-defining condition. Individual studies that highlight the association between HIV and extrapulmonary TB are available. Our objectives were to synthesis evidence on the association between extrapulmonary tuberculosis and HIV and to explore the effective preventive measures of these two diseases.
Methods This is a meta-analysis of observational studies reporting effect estimates on how HIV is associated with extrapulmonary tuberculosis. We searched for the eligible studies in the electronic databases using search terms related to HIV and extrapulmonary tuberculosis. Where possible, we estimated the summary odds ratios using random effects meta-analysis. We stratified analysis by the type of study design. We assessed heterogeneity of effect estimates within each group of studies was assessed using I^2 test.
Results Nineteen studies (7 case control studies and 12 cohort studies) were identified for the present study. The pooled analysis shows a significant association between HIV and extrapulmonary tuberculosis (summary odds ratio: 1.3; 95 % confidence interval (CI) 1.05–1.6; I^2: 0 %). In a subgroup analysis with two studies, a significant association was found between CD4+ count less than 100 and the incidence of extrapulmonary tuberculosis (summary OR: 1.31; 95 % CI 1.02–1.68; I^2: 0 %).
Conclusions Findings show evidence on the association between extrapulmonary tuberculosis and HIV, based on case control studies. Further studies to understand the mechanisms of interaction of the two pathogens are recommended.

Keywords Extrapulmonary tuberculosis · HIV · Risk factor · Meta-analysis

C. Naing (✉) · J. W. Mak · S. F. Wong · A. I. B. M. Kassim
School of Postgraduate Studies and Research, International Medical University (IMU), 57000 Kuala Lumpur, Malaysia
e-mail: cho3699@gmail.com

C. Naing · M. Maung
School of Medical Sciences, IMU, Kuala Lumpur, Malaysia

Introduction

Coexistent tuberculosis (TB) and HIV are known to make TB control difficult especially in high HIV settings. Of the 8.8 million incident cases of TB in 2010, a best estimate of 13 % (1.1 million) are people living with HIV infection (PLH) [1] in resource-limited countries. Both TB and HIV have profound effects on the immune system, because they are capable of disarming the host's immune responses through mechanisms that are not fully understood [2].

Generally, a relatively small proportion of people infected with *Mycobacterium tuberculosis* will develop TB disease [1]. As such, clinically apparent TB develops in approximately 10 % of infected patients, soon after primary infection or years later via reactivation [3]. TB presents with an array of clinical manifestations. It typically affects the lungs (pulmonary TB, PTB) but can affect other sites as well (extrapulmonary TB, EPTB) [1]. A patient with EPTB is defined as a patient with TB of organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges) [4].

Of note is that EPTB has been an AIDS-defining condition, indicating clinical stage 4 in adults [4, 5]. In countries, such as the United States, where PTB and EPTB case counts have both decreased, EPTB has increased as

percentage of total TB cases [5]. Such disproportionate increase highlights the needs to understand the factors contributing to EPTB. However, the increasing rate of EPTB also was reported from countries, such as Saudi Arabia, where prevalence of HIV is relatively very low [6].

The Millennium Development Goals target, which is endorsed by the "Stop TB Partnership" is to reduce the prevalence of TB and to reduce deaths due to TB by 50 % by the year 2015 compared with a baseline level of 1990 [1, 7]. To achieve this target, one component is to scale-up collaborative TB/HIV activities [1, 3]. Although many studies focus on PTB, it appears that studies that address EPTB are relatively limited. Our objectives were to synthesize evidence on the association between EPTB and HIV and to explore the effective preventive measures of these two diseases.

Methods

Search Strategy and Study Selection

To identify eligible studies that address the association between HIV and EPTB, we searched MEDLINE (from 1980 to December 2011) and EMBASE (from 1980 to December 2011) using the following combination of search terms:

#1 extrapulmonary tuberculosis
#2 extrapulmonary TB
#3 gastrointestinal tuberculosis
#4 genitourinary tuberculosis
#5 pleural tuberculosis
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 HIV infections
#8 human immunodeficiency virus
#9 risk factors
#10 cohort study
#11 case control study
#12 epidemiologic study
#13 observational study
#14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 #6 AND #14

We also searched the abstracts of the conferences of the International TB Society (inception to March 2011) and the references of retrieved papers for additional references. Searches were limited to articles about human studies published in English-language journals. For this review, EPTB refers to TB of organs other than the lungs as indicated following WHO criteria [4]. We updated our searches on July 27, 2012.

Inclusion criteria of the studies were met if they (1) were of case–control, cohort, or cross-sectional design; (2) included a comparator group having isolated PTB; (3) include exposure of interest that was serologically confirmed HIV; (4) provided or computed data on relative risk (RR), odds ratio (OR), or hazard ratio (HR) with corresponding 95 % confidence interval (CI); and (5) had performed stratification by age groups. If data were duplicated in more than one study, the most relevant study was included in the present analysis.

Data Extraction

All searches were conducted independently by two investigators. The same two authors independently extracted data on the name of the first author, year of publication, country, study design, number of exposed/unexposed people or cases/controls, adjusted ORs or RRs with 95 % CI, adjustment factors, and methods of confirmation of HIV and EPTB. Any discrepancy was resolved by consensus, and if needed, by consultation with the third author.

Statistical Analyses

We assume that the RR from cohort studies approximates the ORs from case–control studies [8] and HR from cohort studies. We stratified analysis by the type of study design. We assessed heterogeneity of effect estimates within each group of studies using I^2 test, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance [9]. For those studies that reported age, gender, race/ethnicity, or birthplace stratified-specific effects, we entered the ratio measures of the (adjusted) effect as a log OR and the standard error of the log OR using generic inverse-variance weighting method [9], and then included this summary estimate in the meta-analyses.

For robustness of results, we performed sensitivity analyses by the studies with isolated EPTB. To investigate the potential publication bias, we visually examined the funnel plots. Data entry and analyses were carried out with RevMan 5.1.1 (The Nordic Cochrane Centre, 2011).

Results

Description of Studies

Figure 1 provides the flow chart indicating the literature review process. Based on the inclusion criteria, 45 full articles were retrieved and 19 of these were included in final analysis. Some studies were excluded for the following reasons: (1) no provision of specific data on EPTB [10–17]; (2) information on EPTB was insufficient [18–21]; and (3) there was no comparison group for EPTB [22–25]; (4) there were no HIV-positive patients [6, 26–34]. All

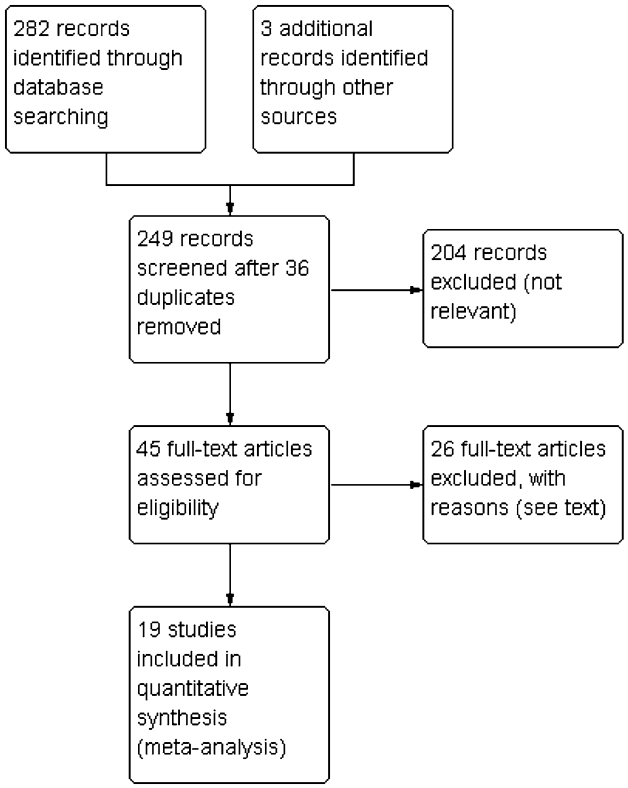

Fig. 1 Flow diagram of the search process for selection of papers

of these 19 studies were published in English. Table 1 presents the characteristics of included studies. These included 7 case control studies (36.8 %) and 12 cohort studies (63.2 %). Seven studies (36.8 %) were performed in the United States [5, 35–40], whereas two (10.5 %) were in Spain [41, 42] and one each (5.3 %) in Africa [43], India [44], Taiwan [45], France [46], Hong Kong [47], Nepal [48], Netherland [49], Switzerland [50], South African [51], and Thailand [52]. Of total TB cases, the highest proportion of EPTB (48.5 %) was reported in Nepal [48], whereas the lowest 12.1 % was in the United States [40]. Regarding the localization of EPTB as reported in the studies that were included for analysis, lymph node involvement was the most frequent site of EPTB [5, 35, 36, 38, 42, 48, 49, 52], followed by pleura [38, 47], bones and joints [40, 45], and urogenital regions [43]. Two studies identified for the current analysis did not mention the specific sites of EPTB infection [41, 46].

Effect Estimations

Figure 2 summarizes the adjusted effect estimates of the 19 studies categorized by the study designs. We did not report the summary effect estimates of the cohort studies due to substantial heterogeneity among studies (I^2: 100 %). The forest plot shows a significant association between HIV and EPTB in the case–control studies regardless of age (summary OR: 1.2; 95 % CI 1.13–1.28; I^2: 0 %).

To identify the relationship between CD4+ counts and the development of EPTB, a subgroup analysis was done with two studies [49, 50], based on available data. A significant association was found between CD4+ count less than 100 and the incidence of EPTB (summary OR: 1.31; 95 % CI 1.02–1.68; I^2: 0 %).

Sensitivity Analysis

After removing a study with children [51], the significant association between HIV and EPTB in the case–control studies was summary OR: 1.3; 95 % CI 1.05–1.6 I^2: 0 %. Regarding the studies having isolated EPTB [5, 37, 46, 47], we could not make the summary estimation because of a substantial heterogeneity among studies (I^2: 100 %).

Regarding the summary measures of the association between EPTB and HIV by site of EPTB, based on the data from four studies [38, 39, 43, 49], the involvement of pleura was only significantly lower risk in HIV-infected EPTB than that of non-HIV-infected patients in a study [48] (OR: 0.76; 95 % CI 0.63–0.82). Based on data from two studies [38, 49], there is no significant increase risk of foreign-born males having HIV-infected EPTB (summary OR: 1.02; 95 % CI: 0.06–1.75; I^2: 0 %; Fig. 2). Funnel plot analysis detected publication bias as the shape of the plots seemed asymmetrical (Fig. 3).

Discussion

EPTB refers to TB outside of the lungs [1, 49]. Studies have reported that although EPTB and PTB case counts have both decreased [5, 49], the reduction in case of EPTB has been smaller [42], resulting in a proportional increase in EPTB compared with PTB [40, 49]. Factors perpetuating EPTB may be poorly recognized compared with those perpetuating PTB [5]. The present study showed evidence on the association between EPTB and HIV based on observational studies. This relationship has biological plausibility and could be explained in the current understanding of pathogenesis of TB. Acquired specific responses to TB is mediated by the orchestrated expansion of cell mediated immunity, which seeks to control (influx of cell mediating portion) and contain (florid influx of macrophages to wall off the infection) [53]. In this context, CD4+ T cell subsets, such as Th 17 cell and FoxP3+ regulatory CD4+ cells, seem to play an important role in containing overall inflammatory response [2, 53] to *M. tuberculosis* antigens. During the emergence of acquired specific responses to mycobacterial infection, the cellular response is mediated by the production of large number of cytokines and chemokines, leading

Table 1 Characteristic of the included studies

	Author and study country	Design	Proportion of EPTB[a]	Site[b]	Adjustment factors	Confirmation of EPTB	Confirmation of HIV
1	Antony et al. [35] USA	CO	61/138 (44.2 %)	Bones and MS	E, G, HIV	Culture-confirmed	Serological test
2	Cailhol et al. [46] France	CC	5,187/18,617 (27.9 %)	NA	A, B, G	NA	NA
3	Castilla et al. [41] Spain	CC	1,256/6,161 (20.4 %)	NA	HIV/AIDS	NA	CD4+ count
4	Fiske et al. [36] USA	CC	564/2,142 (26.3 %)	LN	A, G, HIV, Alc, BCG, IVDU, S	Culture-confirmed (363/564)	NA
5	García-Rodríguez et al. [42]	CO	29/533 (5.4 %)	Pleura	A, B, E, G Alc, HIV, IVDU	Culture and, histological-confirmed	Serological test
6	Gonzalez et al. [37] USA	CO	382[a]/1,878 (28.6 %)	LN	A, E, HIV	Culture-confirmed (382/538)	Serological test (349/538)
7	Gupta et al. [44] India	CO	37[a]/229 (16.2 %)	Disseminated	A, G, DM, HIV	Smear microscopy and/or culture-confirmed or PCR	NA
8	Kherad et al. [50] Switzerland	CC	137/252 (54 %)	LN	A, B, E, G, Alc, HIV, S,	Culture-confirmed	Serological test
9	Kingkaew et al. [52] Thailand	CO	308/769 (40 %)	LN	A, G	Bacteriologically-confirmed&/ culture-confirmed	NA
10	Kipp et al. [38] USA	CC	1,366/6,124 (22.3 %)	Pleura	A, B, G, HIV	Culture-confirmed or acid-fast stain (5,143/6,124)	NA
11	Lin et al. [45] Taiwan	CO	102/766 (13.3 %)	Bone and joint	A, G, DM	Bacteriologically confirmed	NA
12	Madhi et al. [51] Africa	CO	5/137 (3.6 %)	RE	HIV	Bacteriologically and culture-confirmed	Serological test (ELISA)
13	Malkin et al. [43] Africa	CO	90/512 (17.6 %)	Urogenital	HIV	Bacteriologically confirmed	Serological test (ELISA)
14	Noertjojo et al. [47] Hong Kong	CO	790/5,757 (13.7 %)	Pleura	A, DM, HIV	Bacteriologically and culture-confirmed	NA
15	Ong et al. [39] USA	CO	301/1,677 (17.9 %)	LN	A, G	Culture-confirmed	Serological test
16	Peto et al. [5] USA	CO	47,293/ 253,299 (18.7 %)	LN	B, G	Culture-confirmed (34,050/ 47,293)	NA
17	Sreeramareddy et al. [48] Nepal	CO	230/474 (48.5 %)	LN	A, G	Bacteriologically confirmed	NA
18	Te Beek et al. [49] Netherlands	CC	5,042/13,258 (38 %)	LN	A, E, G, HIV	Culture-confirmed	NA
19	Yang et al. [40] USA	CC	85/705 (12.1 %)	Bones and joints	E, G, HIV	Culture-confirmed (83/85)	NA

A age, *B* birth place (country), *CC* case–control study, *Co* cohort study, *E* ethnicity/race, *G* gender, *LN* lymph node, *Alc* alcohol drinking, *BCG* BCG vaccination, *DM* diabetes mellitus, *HIV* human immunodeficiency virus, *IVDU* intravenous drug user, *NA* not available/not mentioned, *MS* muscle, *RE* reticulo endothelial system

[a] EPTB cases/total TB cases

[b] Most common site

to granulomatous inflammatory responses [53] where *M. tuberculosis* is contained and thus potentially prevented from causing active diseases [2, 53]. CD4+ T cells and TNF are important to maintain granuloma organization [2]. The hallmark of HIV infection is the depletion of CD4+ T cells. A dysfunctional T cell population displays loss of functional potential. Hence, granuloma formation may fail in an individual with a compromised immune system. As a result, whereas the majority of adult TB is preferentially confined to the lungs due to the aerobic nature of *M. tuberculosis*, which grows most successfully in tissues with high oxygen content [54], in HIV-infected patients, TB can be a systemic disease involving multiple organs that lack well-defined granulomas [2]. Thus, all forms of EPTB have been described in patients with HIV [2], and as immunosuppression progresses, EPTB becomes increasingly common

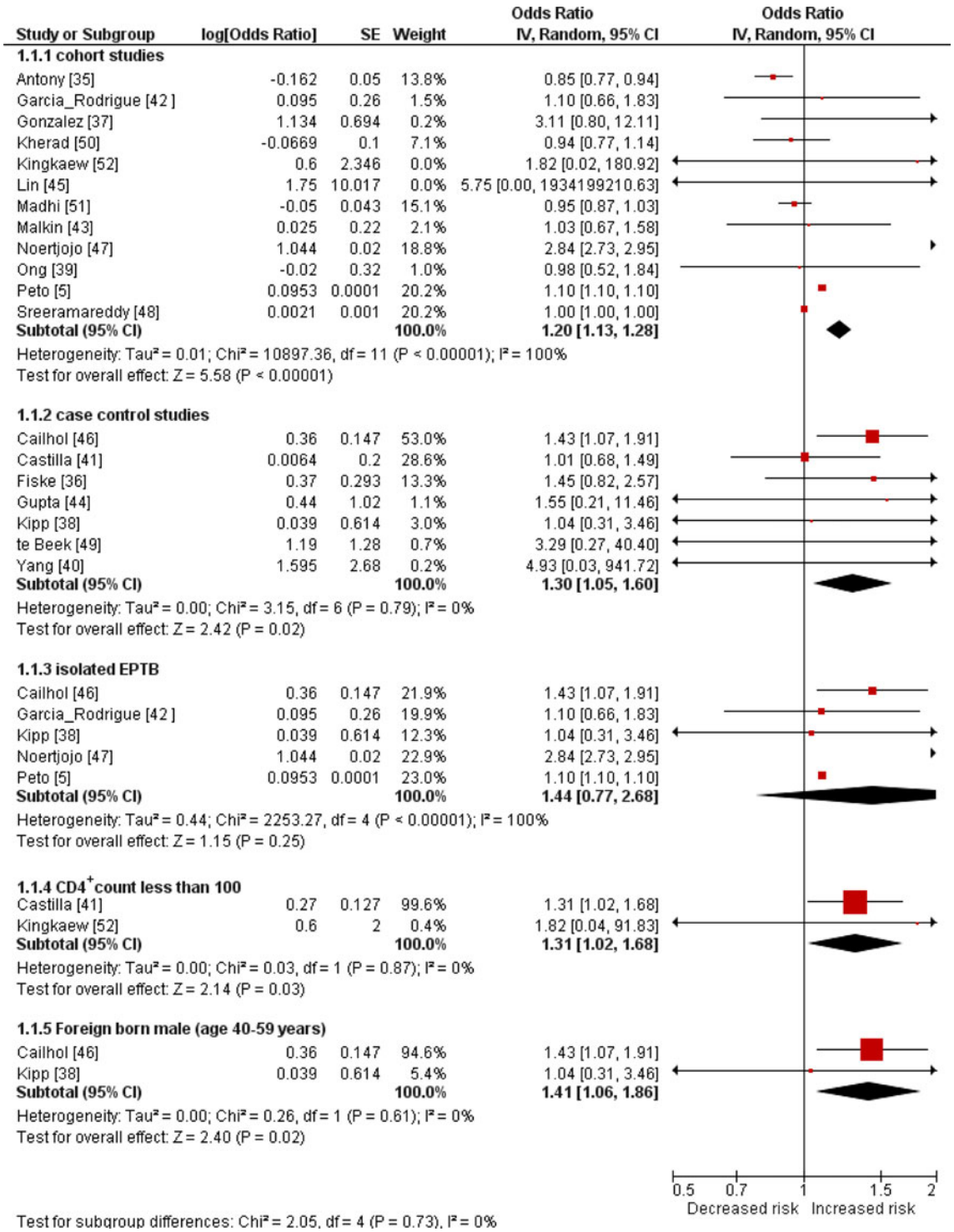

Fig. 2 Forest plot showing risk of HIV in extrapulmonary tuberculosis compared with pulmonary tuberculosis

[55]. Patients with CD4+ count less than 100 who had a higher incidence of EPTB in the present analysis did support this evidence. Also, a study in the United States assessing 320 EPTB cases during a 12-year study period, among HIV-infected patients demonstrated that severe forms of EPTB, such as CNS/meningeal, were independently associated with low CD4+ T cell counts [25].

The current study showed that the involvement of lymph node was the most frequent site of HIV-infected EPTB, followed by pleura. EPTB is a protean disease that can

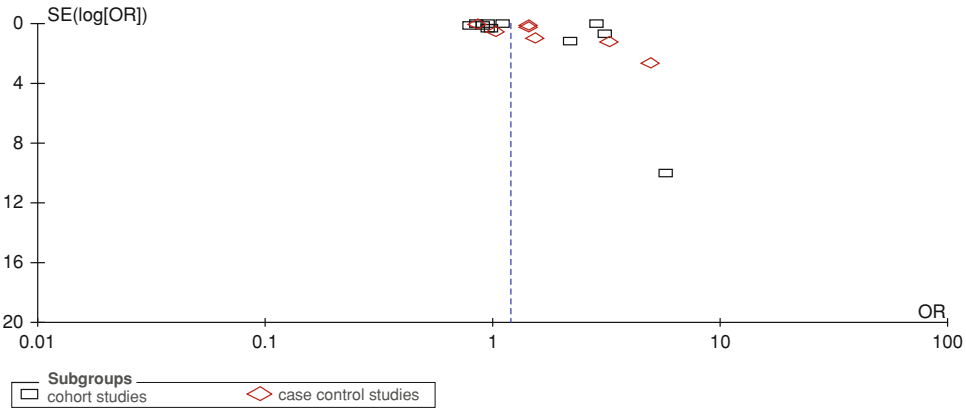

Fig. 3 Funnel plot

involve virtually all organs, including relatively inaccessible sites [37]. It also has been reported that gender differences exist in relation to the common sites of occurrence of EPTB. Lymph node EPTB involvement tends to be more common in women, whereas pleural EPTB is seen more in men [46]. Common wisdom holds, for instance, that pleural TB is a marker of recent acquisition of infection [26, 39]. However, given the importance of the integrity of the delayed-type hypersensitivity response, TB pleuritis would be expected to be more common in HIV seronegative persons and persons with high CD4+ cell counts in the HIV seropositive [39]. Previously published individual studies demonstrated a possible relationship between HIV and EPTB in which cases with concurrent PTB and EPTB were recorded as EPTB in these studies [35, 45]. This may be attributed to the effect of HIV infection on an individual's immune system. Of note is that the progressive decline in immunity may have resulted in the progression of PTB to EPTB [45].

An association exists between EPTB and HIV, which we identified, but it is weak due to the variation in diagnosis and/or defining criteria for EPTB and/or confirmation of HIV status among studies identified for the present review. For instance, some studies that identified patients as having EPTB also included patients with concomitant PTB and EPTB [37, 52], whereas some studies restricted inclusion to patients with isolated EPTB [5, 39, 48, 49]. The impact of this inconsistency in definition of EPTB was documented in a study [5] in which the effect estimate becomes stronger from an RR of 1.1 to 1.7 when liberal diagnosis of EPTB was applied. It was found that some studies did not describe confirmation procedures of EPTB [44] or HIV status [38], or both [46]. As stated earlier, because diagnosis of EPTB in itself often is difficult, EPTB may have been underdiagnosed [47]. Taken together, should there be underreporting, this will lead to insufficient data to provide a weak, but significant, association rather than a stronger association.

Contradictory to the present study, some individual studies reported a high frequency of EPTB in HIV-negative patients [47, 56] even in countries, such as Malawi where HIV prevalence is reportedly high [46, 57]. This suggests that the development of EPTB may be truly unrelated to HIV serostatus [57]. However, patients with an unknown HIV serostatus among the study population may have been interpreted as HIV seronegative, leading to selection bias. We acknowledge the limitation of our estimations; the studies identified for the present analysis were of observational designs and therefore reported crude and adjusted ORs could be biased due to unmeasured or unknown confounders [25]. Regarding the confirmation of EPTB, in the context of diagnosis, EPTB compounds the difficulty imposed by their having a lower frequency of sputum smear positivity [58]. As with earlier reviews [58, 59], a recent systematic review addressing 25 studies showed that the commercial serological tests provided inaccurate and imprecise estimates of sensitivity (range 0–100 %) and specificity (range 59–100 %) for overall EPTB [60]. For lymph node and pleural EPTB, the mean sensitivity was 64 % (range 28–92 %) and 46 % (range 29–63 %), respectively [60]. Misdiagnosis of EPTB is common in all countries and may, therefore, result in unnecessary treatment if falsely diagnosed, or greater morbidity and mortality if the diagnosis is missed, especially in HIV-infected patients [59].

Nevertheless, the association between EPTB and HIV documented in the current study is consistent with presumed pathogenesis and clinical rationale [54, 55], which reinforced our confidence in effect estimation.

Improved recognition of EPTB risk factors may facilitate earlier case detection and treatment, resulting in subsequent reduction in EPTB-associated morbidity and mortality. The positive association between EPTB and HIV documented in the current study implies that TB control program might benefit from a focus on interventions designed to reduce HIV infection and vice versa. Improved understanding of risk factors for EPTB is important to the goal of TB elimination and would enable clinicians to apply a high index of suspicion to the HIV-infected population at risk for EPTB.

Also, a positive diagnosis of EPTB should alert the clinician of a possible HIV-positive status. Similar to earlier studies, the present study acknowledges that HIV and *M. tuberculosis* infections are different and far more complex in coinfected compared with monoinfected patients.

In conclusion, the present meta-analysis indicates that there is evidence for the association between HIV and EPTB based on the case control studies. Further studies to understand the mechanisms of interaction of the two pathogens are recommended.

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Conflict of interest None.

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