Prevalence of extrapulmonary tuberculosis among people living with HIV/AIDS in Southeast Asia: a systematic review and meta-analysis

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Abstract

The dual burden of HIV and tuberculosis (TB) impacts people living with HIV (PLHIV) coinfected with TB. Although some primary studies have been reported on the burden of extrapulmonary TB (EPTB) among PLHIV in Southeast Asia (SEA), there is no systematic review or meta-analysis that attempts to summarize the available literature. Therefore, this review aims to summarize the prevalence of EPTB/HIV co-infection in SEA using meta-analysis based on a systematic review of published articles and gray literature. A comprehensive 3-stage methodology was adopted to conduct a thorough literature search, encompassing both published and gray literature. Data sources such as MEDLINE and Web of Science were searched for articles reporting data from SEA between 2010 and 2022. Findings were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines and were sourced using a predefined search strategy from different databases. The Joanna Briggs Institute prevalence studies checklist was employed for critical appraisal. The meta-analysis of proportions was carried out using the "metaprop" function in R software (version 4.3.1) to generate pooled estimates. Effects were summarized using random-effects models, and sources of heterogeneity were explored through I^2, utilizing subgroup and sensitivity analyses. Publication bias was assessed using funnel plots and pertinent statistical tests, including Egger's regression analysis. A total of 474 studies were initially identified in our search. After the removal of duplicates and a meticulous screening process of titles and abstracts, along with the application of exclusion criteria, 22 studies comprising 34,740 PLHIV were included in the final meta-analysis. The summary effect, or pooled proportion estimate, of EPTB among PLHIV was found to be 18% [95% confidence interval (CI): 15-22; heterogeneity: $\tau 2=0.0056$; degrees of freedom=21, $p<0.001$; I2=99%]. Our study showed that there was a diverse range of prevalence of EPTB among PLHIV in the SEA region, which ranged from 5% (95% CI: 4.0-7.0) in South Korea to 48% (95% CI: 41.0-55.0) in Thailand. Our systematic review and meta-analysis indicate a notably higher prevalence of EPTB among PLHIV. Early diagnosis of EPTB is crucial to mitigating associated morbidity and mortality. Therefore, a thorough medical history and comprehensive physical examination are imperative in assessing PLHIV, aiming to promptly identify and rule out EPTB. After a diligent evaluation, appropriate diagnostic measures and tailored management strategies should be promptly instituted.

Introduction

Tuberculosis (TB), which has surpassed HIV/AIDS as the most prevalent infectious disease, is the ninth most common cause of

death worldwide. TB that affects organs other than the lungs, such as the pleura, lymph nodes, abdomen, genito-urinary system, skin, joints, bones, and meninges, is referred to as extrapulmonary TB (EPTB) [1,2].

Approximately 10.6 million individuals [95% confidence interval (95% CI): 9.9-11 million] experienced TB globally in 2021. Notably, the Southeast Asia (SEA) region accounted for a substantial portion, with an estimated 4.8 million people having TB during the same period. Of these, an estimated 0.7 million people worldwide and 0.1 million people in the SEA region were identified as people living with HIV (PLHIV) coinfected with TB [3]. According to the Global TB Report of 2020, among the 7.5 million reported cases of TB worldwide, 16% presented with EPTB globally, with the proportion rising to 19% specifically in the SEA region [4].

The World Health Organization (WHO) is actively engaged in addressing the impact of co-infection between HIV and EPTB through strategic interventions. In 2007, the WHO issued recommendations for diagnosing EPTB in PLHIV, emphasizing the significance of a single specimen testing positive for culture, histological evidence, or compelling clinical indicators of active EPTB [5]. Furthermore, in 2012, the WHO updated its strategy for joint TB/HIV initiatives [6], emphasizing the critical importance for all countries to monitor the prevalence of HIV among TB patients and *vice versa*. This highlights the ongoing commitment to enhancing comprehensive care for individuals facing the challenges of dual infections.

Various SEA countries have reported a wide range of estimates regarding the prevalence of EPTB among PLHIV. For instance, studies conducted in India indicate a prevalence range of 11-68% [7-12], and in Thailand, 40% of PLHIV were found to have co-infection with EPTB [13]. In sub-Saharan Africa, a systematic review revealed prevalence estimates of EPTB among PLHIV ranging from 6.4% (95% CI: 3.8-9.0) to 36.8% (95% CI: 28.6-45) [14].

Despite this, high-quality estimates of EPTB prevalence among PLHIV remain elusive, and no systematic review has been conducted among this population in the SEA region to date. To address this gap and gain insights into the dual burden of TB/HIV, our study aims to comprehensively summarize and synthesize the prevalence of EPTB among PLHIV in the SEA region. This effort is crucial for informing and developing effective public health strategies to meet the unique needs of individuals dealing with both EPTB and HIV/AIDS.

Methodology

Study design and population

Conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15], we systematically reviewed a range of studies investigating the prevalence of EPTB among PLHIV. This review encompassed all primary studies from SEA countries that reported EPTB prevalence among PLHIV. The study population comprised all age groups and genders. Diagnosis of EPTB occurred either during the initial screening, before commencing antiretroviral therapy, or at the initiation of antiretroviral therapy.

Search strategy

Employing a 3-stage methodology, the search technique was designed to comprehensively identify relevant published and grey literature, that is not published in a commercial publication, including academic papers, theses and dissertations, research reports, conference papers, and ongoing research. Initially, a targeted search was conducted on Medline and Web of Science databases, analyzing text words from titles and abstracts, along with index keywords characterizing each article. Subsequently, a second search encompassed all pertinent databases using identified keywords and index phrases. The third phase involved reviewing reference lists of key articles for additional studies.

The search was focused on Medline and Web of Science databases, utilizing initial keywords and Medical Subject Headings terms for the Medline database. The specified search terms covered various aspects of TB, including different anatomical sites, and incorporated HIV-related terms. The geographical focus was on SEA, encompassing countries such as India, Bangladesh, Nepal, Sri Lanka, Maldives, Myanmar, Bhutan, Thailand, Indonesia, Democratic Republic of Korea, and Timor-Leste.

The search terms included: "Tuberculosis, lymph node" OR "tuberculosis, cardiovascular" OR "tuberculosis, central nervous system" OR "tuberculosis, cutaneous" OR "tuberculosis, endocrine" "tuberculosis, gastrointestinal" OR "tuberculosis, hepatic" OR "tuberculosis, ocular" OR "tuberculosis, oral" OR "tuberculosis, osteoarticular" OR "tuberculosis, pleural" OR "tuberculosis, splenic" OR "tuberculosis, urogenital" OR "tuberculosis"

AND "HIV" OR "AIDS" OR "human immunodeficiency virus" OR "acquired immunodeficiency syndrome" OR "co-infection" OR "opportunistic infection" OR "opportunistic" AND "South-east Asia" (India, Bangladesh, Nepal, Sri Lanka, Maldives, Myanmar, Bhutan, Thailand, Indonesia, Democratic Republic of Korea and Timor-Leste).

Eligibility criteria

Inclusion criteria mandated that studies should be in the English language and have a publication date falling between January 1st, 2010, and December 31st, 2022.

The population of interest consisted of PLHIV, with EPTB considered as the exposure. No specific comparison was undertaken, and the outcome of interest was the prevalence of EPTB among PLHIV.

The studies included in the review focused on PLHIV as the primary subject, where EPTB was reported as a proportion of all TB coinfected cases. Prevalence was either recorded or calculated within the subset of PLHIV. Encompassing cohort studies (both prospective and retrospective), cross-sectional studies, and medical reviews, the selected studies were reported from various health facilities, including HIV care and treatment centers, TB care centers, tertiary care hospitals, and private clinics.

Exclusion criteria involved abstracts lacking full texts, articles missing journal names and/or authors, studies with a small sample size of less than 30 individuals, those without reported prevalence and exclusively reporting incidence, case studies, qualitative reviews, and studies without segregation of pulmonary TB and EPTB. This refined selection criterion aimed to ensure the inclusion of high-quality studies for comprehensive analysis.

Methods of extrapulmonary tuberculosis screening and/or diagnosis among people living with HIV

As per the WHO consolidated guidelines on TB [4], and the national guidelines, PLHIV were screened for symptoms based on the presentation and either of the following methods were used for the final diagnosis depending on the site of EPTB: microscopy or

sputum culture, GeneXpert, X-ray, ultrasonography, fine needle aspiration of fluids following the cytology, histopathology, broncho-alveolar lavage, cerebro-spinal fluid analysis, *etc*.

Outcome

This review looked at studies from SEA that estimated the prevalence of EPTB among PLHIV.

Study selection

Two researchers (AH and RM) independently appraised the studies. Primary screening was done through titles and abstracts review, and then duplicates were removed. Secondly, a full-text review of articles was done to identify eligible articles. Finally, methodological critical appraisal was done using the Joanna Briggs Institute (JBI) tool [16]. The final identified studies were then included for systematic review and meta-analysis.

Methodological quality assessment

The chosen articles underwent a standardized critical appraisal process using a tool from the JBI to assess the risk of bias [16]. Quality assessment was independently conducted by two researchers (AH and RM), with any disagreements resolved through discussions and, when necessary, thorough consultation with a third researcher (AC). The checklist, which considered aspects such as study setting, sample collection methods, diagnostic criteria, and the validity and reliability of measurements, was employed. Only studies with optimal scores based on this appraisal were included in the systematic review.

Data collection and extraction

To select studies, we meticulously reviewed high-quality papers using the JBI critical appraisal tools. The data extracted for inclusion in our review encompassed all information relevant to the research question, meeting the criteria for potential meta-analysis and narrative synthesis of results. Key variables, including the country of study, prevalence of EPTB, and the number of PLHIV with and without TB, were considered. In cases where data were unclear or missing from the published study, we proactively contacted the respective authors to obtain the necessary details. Furthermore, the data extraction process underwent independent cross-checks to ensure accuracy, and a summary estimate was employed for presenting the results.

Data analysis and statistical methods

Calculation of prevalence was done using the numerator as the number of EPTB cases, and the denominator was taken as the total number of PLHIV. In six studies, the prevalence value was not directly reported in the text. Thus, prevalence was calculated from these studies by considering the reported number of EPTB cases as the numerator and the number of PLHIV as the denominator.

All statistical analyses were performed by R software (version 4.3.1), and the function "metaprop" was adopted to conduct the meta-analysis of proportions to generate pooled estimates.

The degree of heterogeneity among the included studies was evaluated using R software. We measured statistical heterogeneity using the I^2 statistic, p-values, degree of freedom (df), and by visually inspecting forest plots, which also described the total variation among the studies that were inconsistent.

We also used the inverse variance method, Der Simonian-Laird estimator for tau (τ^2), Jackson method for CI of τ and (τ^2), untransformed proportions, and Clopper-Pearson CI for individual studies. Summary tables and narrative prose are used to present the characteristics of the studies included. Pooled prevalence estimates for the pre-specified outcomes of interest were derived using random effects meta-analytic methods and reported in forest plots in anticipation that prevalence varies between studies and communities. We used a random-effects model, which helps us in checking with and between study variations using Kendall's τ^2 [17].

Following the identification of eligible studies for review, we conducted subgroup analyses focusing on countries in SEA and the study designs employed for diagnosing EPTB. To assess publication bias, we utilized a funnel plot and conducted statistical tests, including Egger's regression analysis [18]. A forest plot was employed to summarize the effect size in summary estimates. The reporting of the study flow adhered to the PRISMA standard guidelines (Figure 1).

Results

Study characteristics

Initially, 474 studies were identified. Of these, 111 duplicates were excluded, and 363 studies were eligible for screening. Of these, 273 studies were further excluded after reviewing the title and abstract, leaving 90 studies for full-text review. Following the full-text review, 22 studies [12,13,19-39] with 34,740 PLHIV were finally included for investigation. The PRISMA flow diagram is presented in Figure 1. The characteristics of the studies are given in *Supplementary Table 1*.

Methodological quality assessment of included studies

The methodological evaluation of the studies employed the JBI critical appraisal tool [16], which assesses the methodological quality by considering potential bias, study design, conduct, and analysis. Two researchers (AM and RM) rigorously appraised all selected studies. Out of the 22 studies, 15 obtained a score of 9 out of 9, while the remaining 7 studies scored 8 out of 9. This overall appraisal deemed them suitable for inclusion in the review.

Studies surpassing the mean for optimal quality, with a majority of "yes" responses, were included, as indicated in Table 1.

Meta-analysis

The primary objective of the meta-analysis was to provide a summary of the prevalence and corresponding 95% CI of EPTB among PLHIV in the SEA region.

Upon conducting the meta-analysis, data from 34,740 PLHIV were scrutinized to estimate the prevalence of EPTB, with 5229 PLHIV identified as having EPTB in the review. The meta-analysis yielded a summary effect or pooled proportion estimate for the prevalence of EPTB among PLHIV, indicating a value of 18% (95% CI: 15-22). The analysis also revealed significant heterogeneity ($\tau2$=0.0056; df=21, p<0.0001; I^2=99%) (Figure 2).

Sensitivity analysis

For the statistical validity to check the variations in prevalence, subgroup analysis was carried out using R software (version 4.3.1).

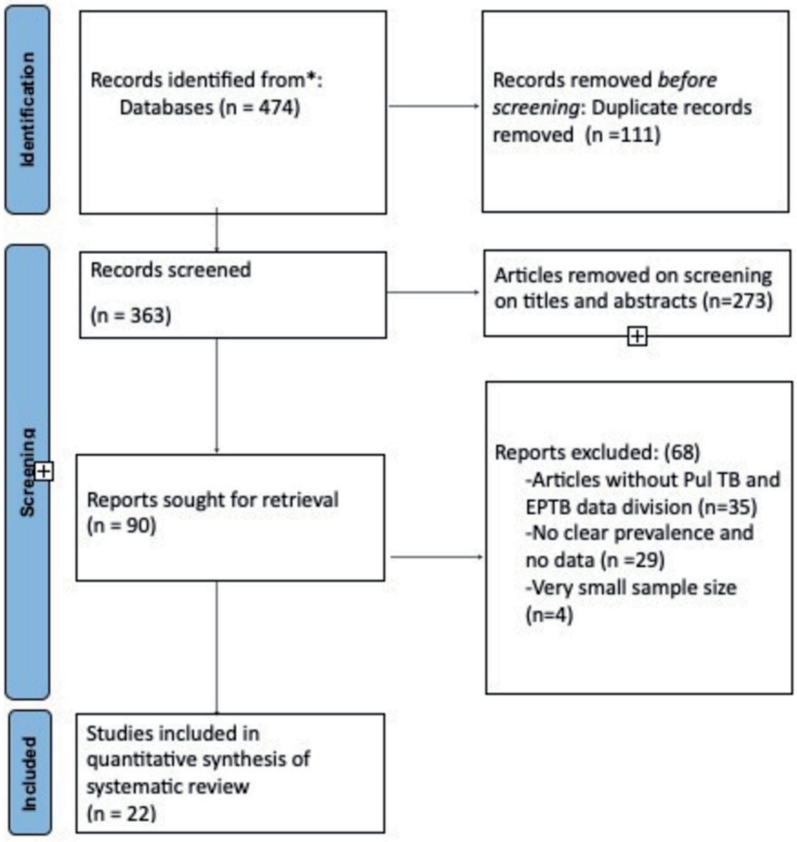

Figure 1. PRISMA Flow diagram of the study search, selection, and screening of literature for the review. The review encompassed 22 studies with a cumulative sample size of 34,740 participants, representing a collective data pool from nine countries. 14 studies were from India, 2 from Nepal, and 1 each from other countries of the SEA region. TB, tuberculosis; EPTB, extrapulmonary tuberculosis.

able 1. Critical appraisal results of studies included in the systematic review and meta-analysis by the Joanna Briggs Institute prevalence critical appraisal checklist.

S. No	Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total
1	Bishnu *et al.* [19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
2	Das *et al.* [33]	Y	Y	Y	Y	N	Y	Y	Y	Y	8
3	Das *et al.* [30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
4	Hiregoudar *et al.* [34]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
5	Hong yien Tan *et al.* [35]	Y	Y	N	Y	Y	Y	Y	Y	Y	8
6	Kamath *et al.* [36]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
7	Kapadiya *et al.* [37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
8	Karmakar *et al.* [24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
9	Khanal *et al.* [32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
10	Lee *et al.* [38]	Y	Y	Y	Y	Y	N	Y	Y	Y	8
11	Matin *et al.* [39]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
12	Parchure *et al.* [20]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
13	Poudel *et al.* [21]	Y	Y	N	Y	Y	Y	Y	Y	Y	8
14	Phyo *et al.* [22]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
15	Kim *et al.* [23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
16	Sharma *et al.* [12]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
17	Shastri *et al.* [25]	Y	Y	Y	Y	Y	N	Y	Y	Y	8
18	Songkhla *et al.* [26]	Y	N	Y	Y	Y	Y	Y	Y	Y	8
19	Spalgais *et al.* [27]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
20	Srirangaraj *et al.* [28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
21	Weber *et al.* [29]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
22	Witaningrum *et al.* [31]	Y	Y	N	Y	Y	Y	Y	Y	Y	8

EPTB, extrapulmonary tuberculosis; JBI, Joanna Briggs Institute; Y, yes; N, no; SEA, Southeast Asia region.

Subgroup analysis

Subgroup analysis was conducted to explore heterogeneity based on both study designs and countries with more than two studies (Table 2). The studies were categorized into two groups: the first group was based on study design, and the second group was based on the countries involved. Notably, studies from India constituted one group, while the remaining countries formed another group since there were no countries with more than two studies in the latter.

Regarding study design heterogeneity, three groups emerged, including retrospective studies (9 studies), cross-sectional studies (5 studies), and prospective cohort studies (8 studies). Minimal variation was observed, with the prevalence of EPTB being 18% (95% CI: 13-23), 17.8% (95% CI: 7.3-28.2), and 19% (95% CI: 14.0-24.0), respectively.

Similarly, the grouping was done based on the countries involved. One group with 13 studies exclusively comprised data from India, while all other studies formed a separate group due to the absence of any other country with more than two studies in the selected dataset. A notable variation was observed in this subgroup analysis. Studies from India demonstrated a prevalence of 21.5 (95% CI: 16.4-26.6), while the other group exhibited a prevalence of 12.8 (95% CI: 9.8-15.8).

Proportion of extrapulmonary tuberculosis among all tuberculosis cases

We further analyzed the proportion of EPTB among all reported TB cases in PLHIV. To calculate this, the numerator included all identified EPTB cases, while the denominator comprised all reported TB cases in the studies identified for the systematic

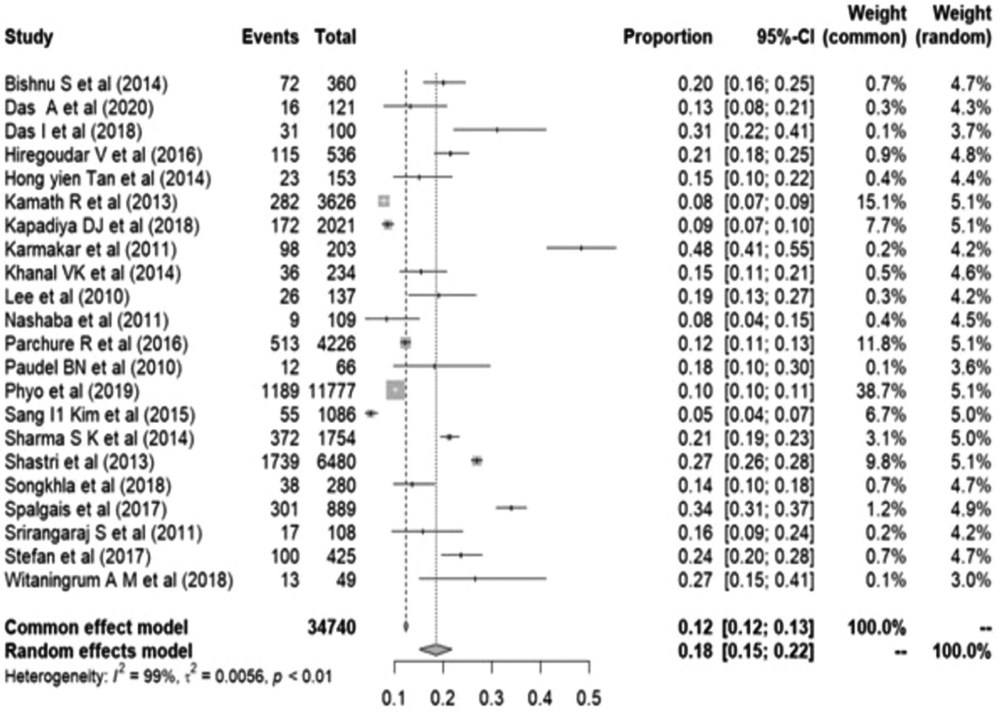

Figure 2. Forest plot showing the proportion of extrapulmonary tuberculosis among People living with HIV in the Southeast Asia region. CI, confidence interval.

Table 2. Heterogeneity assessment summary by using sensitivity and subgroup analysis.

Subgroup analysis	Number of studies	Prevalence of EPTB (95% CI), random-effects model	τ^2	I^2 (%)	p
Overall	22	18 (15, 22)	0.0056	98.6%	<0.0001
By study design					
Retrospective study	9	18 (13, 23)	0.0055	98.0	<0.0001
Cross-sectional study	5	17.8 (7.3, 28.2)	0.0137	99.2	<0.0001
Prospective cohort study	8	19 (14.0, 24.0)	0.0046	97.1	<0.0001
By countries having >2 studies					
India	13	21.5 (16.4, 26.6)	0.0084	99	<0.0001
Others including Nepal	9	12.8 (9.8, 15.8)	0.0014	90.2	<0.0001

CI, confidence interval; EPTB, extrapulmonary tuberculosis.

review (Table 3). During the meta-analysis, data from 14,150 TB cases among PLHIV were assessed to estimate the proportion of EPTB in all TB cases. Specifically, 5229 PLHIV were identified as having EPTB in the review. The summary effect or pooled proportional estimate from the meta-analysis for the proportion of EPTB among TB cases in PLHIV was determined to be 49.5% (95% CI: 42-57). The analysis revealed significant heterogeneity ($\tau 2$= 0.0287; df=21, p<0.001; I^2=98.5%), as depicted in Figure 3.

Table 3. Proportion of extrapulmonary tuberculosis cases among all tuberculosis cases from selected studies for systematic review and meta-analysis.

S. No	Study	Country	Population characteristics	Sample size or total PLHIV included	Events (EPTB)	Total TB cases	Proportion of EPTB
1	Bishnu *et al.* (2014) [19]	India	PLHIV >18 years	360	72	111	65
2	Das *et al.* (2020) [33]	India	PLHIV >18 years	184	16	35	46
3	Das *et al.* (2018) [30]	India	PLHIV >18 years	100	31	55	56
4	Hiregoudar *et al.* (2016) [34]	India	PLHIV >15 years	536	115	206	56
5	Hong yien Tan *et al.* (2014) [35]	Malaysia	PLHIV >18 years	153	23	78	29
6	Kamath *et al.* (2013) [36]	India	PLHIV >18 years	3626	282	684	41
7	Kapadiya *et al.* (2018) [37]	India	PLHIV >18 years	2021	172	360	48
8	Karmakar *et al.* (2011) [24]	India	PLHIV >18 years	224	98	123	80
9	Khanal *et al.* (2014) [32]	Nepal	PLHIV >18 years	234	36	87	41
10	Lee *et al.* (2010) [38]	South Korea	PLHIV >18 years	2548	26	134	17
11	Matin *et al.* (2011) [39]	Bangladesh	PLHIV >18 years	109	9	23	30
12	Parchure *et al.* (2016) [20]	India	PLHIV >18 years	4226	513	691	63
13	Poudel *et al.* (2010) [21]	Nepal	PLHIV >18 years	66	12	22	73
14	Phyo et al (2019) [22]	Myanmar	PLHIV >15 years	11777	1189	3370	34
15	Sang I Kim *et al.* (2015) [23]	Korea	PLHIV >18 years	1086	55	210	69
16	Sharma *et al.* (2014) [12]	India	PLHIV >18 years	1754	372	507	58
17	Shastri *et al.* (2013) [25]	India	PLHIV >18 years	6480	1739	6498	27
18	Songkhla *et al.* (2018) [26]	Thailand	PLHIV >18 years	399	38	118	71
19	Spalgais *et al.* (2017) [27]	India	PLHIV >18 years	1064	301	320	59
20	Srirangaraj *et al.* (2011) [28]	India	PLHIV, >18 years	108	17	158	81
21	Stefan *et al.* (2017) [29]	India	PLHIV >16 years	425	100	285	35
22	Witaningrum *et al.* (2018) [31]	West Papua	PLHIV >18 years	49	13	16	81

PLHIV, people living with HIV; EPTB, extrapulmonary tuberculosis.

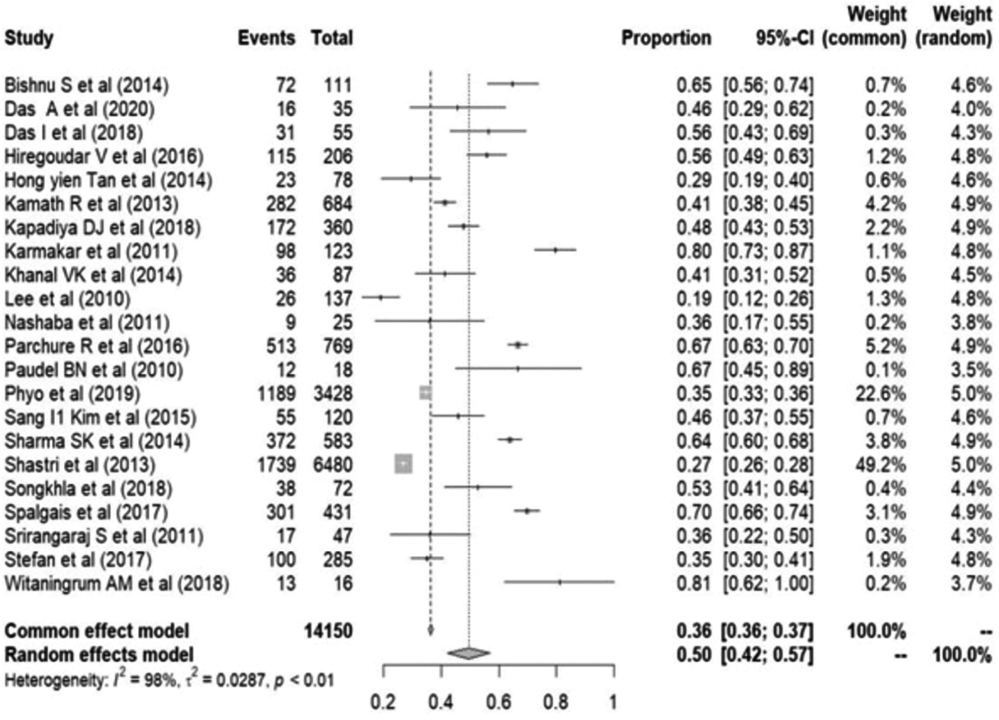

Figure 3. Forest plot showing the proportion of extrapulmonary tuberculosis out of all tuberculosis patients among People living with HIV in the Southeast Asia region. CI, confidence interval.

Publication bias

Publication bias was assessed using linear regression tests through funnel plot and regression tests with random-effects models for identified studies (Figure 4). There was no publication bias. In addition, statistical tests were performed, and again, no evidence of publication bias was observed (Egger's linear regression test of funnel plot showed a p-value of 0.0710) [18].

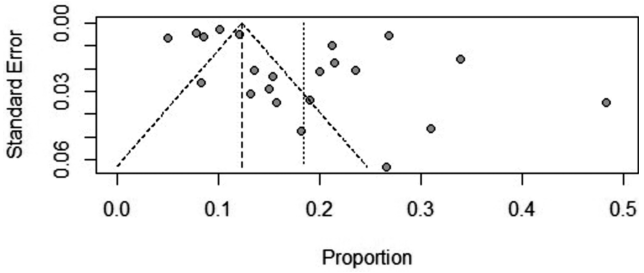

Figure 4. Funnel plot depicting effect sizes for selected studies against the pooled effect size's standard error.

Discussion

To the best of our knowledge, this is the first comprehensive systematic review and meta-analysis focusing specifically on the prevalence of EPTB among PLHIV in the SEA region. In this review, 22 studies published between 2010 and 2022 were included. This review estimated the pooled prevalence of EPTB among PLHIV in SEA. In the meta-analysis, data of 34,470 PLHIV were reviewed as a sample to estimate the prevalence of EPTB. The summary effect or pooled proportion estimate of meta-analysis of EPTB among PLHIV was found to be 18% (95% CI: 15-22).

Our study showed a diverse range of prevalence of EPTB among PLHIV in the SEA region, ranging from 8% (95% CI 4.0-15.0) in India and Bangladesh to 61% (95% CI 55.0-67.0) in Thailand. The prevalence of EPTB among PLHIV from Indian studies out of those selected for final review (14 out of 22) ranged from 8% (95% CI 4.0-15.0) to 48% (95% CI 41.0-55.0). The study from Thailand showed the prevalence of 61 %; the higher prevalence can be explained by higher HIV prevalence in Thailand and active screening in public health settings [13]. A key limitation was the scarcity of studies identified during the review process. Few studies exist that address the prevalence of EPTB among PLHIV using rigorous scientific methodologies for data collection and analysis.

A similar systematic review done in the sub-Saharan African region reported the prevalence of EPTB in the range of 6.4 % (95% CI 3.8-9.0) to 36.8 % (95% CI 28.6-45.0) [14].

In India and other countries globally where TB is endemic, TB is acquired in childhood. The risk of TB is quite high in PLHIV, which is around 16-21 times that of a person without HIV infection [40]. HIV and TB influence each other. The impact of HIV is such that the risk of developing TB is much higher (16-27 times) in PLHIV [41]. Similarly, the inflammatory response to TB bacilli increases HIV replication. Thus, a person having dual infection has higher chances of mortality and morbidity [42].

Clinical presentation of EPTB varies greatly from non-specific signs and symptoms (for example, ascites, pleural effusion, and gibbus deformity) to organ- and system-specific symptoms based on the site involved. The classic symptoms of TB may present in PLHIV having PTB, but EPTB presents variably. The majority of PLHIV coinfected with EPTB have negative sputum smear, leading to improper diagnosis of EPTB and under-treatment. Nearly 45% PLHIV with coinfected sero-negative TB are expected to die, which is quite alarming [43].

Clinical manifestation of EPTB depends on the system involved and includes meningitis, lymphadenitis, musculoskeletal, urogenital, abdominal, cutaneous, miliary TB, *etc*. Diagnosis of TB is mainly by symptom screening and further confirmed with nucleic acid amplification tests or by culture. Diagnosis of EPTB is challenging as most of the cases present with constitutional symptoms or specific symptoms based on the system involved [44].

Our analysis revealed that the proportion of EPTB among all TB cases in PLHIV was 49.5% (95% CI: 42-57). This highlights a higher prevalence of EPTB among PLHIV compared to the general population. In the general population, the proportion of EPTB is typically around 20%, whereas among PLHIV, it is approximately 40% [8].

The WHO has acknowledged a data gap concerning EPTB, attributing it to the fact that a significant number of cases are managed outside the public sector [40]. While India's HIV care and treatment guidelines indicate an approximate EPTB proportion of 40% among all TB cases [42], there has been a notable gap in understanding the prevalence of EPTB among PLHIV in the SEA region [8].

In accordance with the WHO End TB Strategy of 2016, the overarching objective for TB control is to bring an end to the TB epidemic in the Region by 2035 [40]. This entails implementing improved diagnostic methods and ensuring timely screening and treatment of EPTB cases. The achievement of this goal hinges on effectively addressing and managing EPTB, without which the overall objective becomes unattainable.

Sensitivity analysis including subgroup analysis

Sensitivity analysis was done based on the subgroups (Table 2). In this meta-analysis, significant heterogeneity was noted. This heterogeneity may arise from differences in populations across the 11 different SAE countries, different study designs, outcome reporting differences, and variations in the definition and terminology of EPTB across studies or countries. Consequently, a random effects model was used for our meta-analysis. Subgroups belonging to Indian studies showed a higher prevalence as compared with the subgroups of other countries. This might be explained by the higher incidence of TB in the Indian sub-continent [45].

Anticipated variations were foreseen due to factors such as the clinical site of EPTB, the specific organ involved, and the settings where laboratory investigations were conducted. However, performing subgroup analysis based on these factors proved challenging. Nevertheless, subgroup analysis was conducted based on study designs. It is essential to acknowledge that within the reviewed studies, certain ones adopted a retrospective design, which could potentially lead to an underestimation of the prevalence of EPTB among PLHIV.

Bias

In our overall review, a potential source of bias could be selection bias due to the inclusion of study sites predominantly being outpatient units or tertiary care centers. Patients with signs and symptoms are more inclined to seek care at these facilities compared to those without any apparent issues. However, this potential bias is

mitigated by the extended, long-term nature of HIV treatment. Given that PLHIV typically visit care and treatment centers monthly or every 3 months for treatment, it is likely that they would undergo screening regardless of the presence or absence of signs and symptoms.

Additionally, there is the potential for selection bias, particularly in studies with a retrospective design, accounting for 9 out of the 22 studies. The inclusion criteria involved incorporating studies with complete data, necessitating the exclusion of records with incomplete data due to non-response or missing variables. This process introduces the possibility of selection bias. Similarly, there may be associated information bias as data abstraction in studies was conducted without the use of standardized checklists piloted before abstraction [46]. In effect, the prevalence of EPTB among PLHIV might be underestimated due to these considerations.

Publication bias that was assessed using a linear regression model gave a p-value of 0.0710, which shows that there was no publication bias. However, there were few studies whose sample size was not large, and that was the reason for not having all the identified studies near the tip of the funnel in the estimated figure (Figure 4). Nevertheless, it did not show any significant publication bias.

However, the dual challenge of HIV and TB in SEA has bolstered the significance of our study review. One limitation stems from the varied diagnostic methodologies employed for diagnosing EPTB among PLHIV. Given potential inter-country variations, conducting an analysis based on different diagnostic modalities fell beyond the scope of this study. Despite this, it is noteworthy that all national guidelines align with the recommendations and guidelines set forth by the WHO. Another limitation is the inclusion of studies exclusively in English, suggesting that future, more exhaustive research could be undertaken to address this linguistic constraint.

Conclusions

We can conclude from our systematic review and meta-analysis that the prevalence of EPTB among PLHIV was high. It is important to diagnose EPTB early enough to reduce the morbidity and mortality associated. It is necessary to take a good history and a robust physical examination to rule out EPTB among PLHIV, which should be followed by appropriate diagnosis and management accordingly. We recommend conducting updated systematic reviews and meta-analyses that incorporate more recent studies to enhance the robustness and generalizability of the findings.

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Online supplementary material:

Supplementary Table 1. Characteristics of the studies included in the systematic review and meta-analysis from Southeast Asia.