



Candida coinfection among patients with pulmonary tuberculosis in Asia and Africa; A systematic review and meta-analysis of cross-sectional studies

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ABSTRACT

Diagnosis of fungal co-infections in patients suffering from pulmonary tuberculosis has critical importance. Therefore, we aimed to determine the prevalence of candida coinfection in patients with pulmonary tuberculosis.

The present systematic review of cross-sectional studies was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) Protocol. Studies published online in English from January 2001 to March 2019 were assessed. Literature search was done in Web of Science, MEDLINE/PubMed, and Scopus databases and search engines using keywords combinations of “pulmonary fungi”, “pulmonary coinfection”, OR “pulmonary mycosis”, “pulmonary fungal infections/agents”, OR “polymicrobial infection”, OR “secondary infection”, OR “mixed infections”, “pulmonary candidiasis”, “fungi coinfection”, “fungal co-colonization”, AND “pulmonary tuberculosis”, OR “pulmonary TB”, AND “Asia”, AND “Africa”. Data was analyzed using Comprehensive Meta-Analysis software (CMA). Heterogeneity between studies was evaluated by Cochran's Q and I² tests.

The pooled prevalence of *Candida* coinfection among patients with pulmonary tuberculosis was 25.7% (95% CI: 23.7–27.9). *C. albicans* was the most prevalent *Candida* spp. with a pooled prevalence of 65.8% (95% CI: 54.3–75.7). Risk factors of candida coinfection were smoking, diabetes, advanced age, and low body mass index.

The present review showed a high rate of candida coinfection among patients suffering from pulmonary tuberculosis. So, appropriate measures are necessary to early diagnose and treat these infections.

1. Introduction

Fungal co-infections are of critical importance in individuals receiving antibiotics and/or corticosteroids due to immunodeficiency disorders such as AIDS or severe pulmonary diseases such as tuberculosis (TB) [1]. Undiagnosed opportunistic fungal infections may even lead to death; particularly in patients with compromised immune system [2]. Patients with tuberculosis are immunocompromised and susceptible to fungal and lungs mycotic infections [3].

Generally, up to 1 million people recovered from tuberculosis develop concomitant fungal infections annually which are often misdiagnosed as relapsed TB [4].

In 2018, there were an estimated 10 million new TB cases worldwide, with prevalence of 5.7 million men, 3.2 million women and 1.1 million children. Individuals living with HIV accounted for 9% of the

total [5]. Furthermore, totally, the TB mortality rate fell by 42% between 2000 and 2018 and TB deaths decrease by 38% in the same period [6].

Depending on the population studied and methods used for isolating fungi, candida species have been identified in 3–84% of sputum specimens. The prevalence of candida coinfection has been reported in 15–32% of patients with pulmonary tuberculosis [1].

The main risk factors of primary and secondary fungal pulmonary coinfection in TB patients include immunodeficiency due to mucosal or cutaneous barrier disruption, using broad-spectrum antibiotics and steroids, premature birth, hemodialysis, cytotoxic chemotherapy, tissue transplantation, chronic diseases, neutropenia, defects in the function of innate or cell-mediated immunity, metabolic syndrome, solid and hematologic malignancies, advanced age, recent radiation therapy, burns, prolonged hospitalization, severe trauma, bacterial infections,

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recent surgery, and implanted central intravascular access devices [7].

Unspecific clinical manifestations deter the diagnosis of fungal pulmonary co-infections imposing patients with tuberculosis at high risk of morbidity and mortality [8]. In particular, fungal infections caused by *Candida* render relatively higher rates of morbidity and mortality [9]. Infections caused by fungi are responsible for death of about 1.5 million people annually. More than 90% of all fungal-associated deaths are caused by four main genera including *Cryptococcus*, *Candida*, *Aspergillus*, and *Pneumocystis* [10].

Candida albicans is a potentially pathogenic fungi causing very mild to severe invasive mucocutaneous infections, particularly in immunocompromised individuals [11]. *Candida* species comprise the fourth main causes of nosocomial bloodstream infections (BSI) and are responsible for 8%–10% of all hospital acquired BSIs in the United States [12]. Therefore, it is important to focus on co-infections of these saprophytic organisms, especially in patients with pulmonary tuberculosis [13].

Recently, the incidence of infections caused by non-*albicans Candida* spp. has increased [4]. Most of these organisms show resistance to routine antifungal drugs [14]. On the other hand, accurate identification of *Candida* species is necessary to appropriately select antifungal agents and treat invasive candidiasis [15]. Concerning the significance of concurrent candidiasis in patients with tuberculosis and the lack of a comprehensive review on this issue, the present systematic review and meta-analysis aimed to determine the prevalence of candidiasis caused by different *Candida* species in patients with pulmonary tuberculosis in Asia and Africa.

2. Materials and methods

2.1. Search strategy

The present systematic review of cross-sectional studies was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) Protocol (File1). A systematic literature search was conducted in Web of Science, MEDLINE/PubMed, Scopus, Google Scholar, Cochrane Library, and Science Direct databases. Studies published between January 2001 and March 2019 was collected. Medical subject headings (MeSH) and non-MeSH keywords were searched within titles, abstracts or keywords: Search strategy was as “pulmonary fungi”, “pulmonary coinfection”, OR “Pulmonary mycosis”, “pulmonary fungal infections/agents”, OR “Polymicrobial infection”, OR “Secondary infection”, OR “Mixed infections”, “pulmonary Candidiasis”, “fungi coinfection”, “Fungal co-colonization”, AND “pulmonary tuberculosis”, OR “pulmonary TB”, AND “Asia”, AND “Africa”. Only studies published in English were included. The literature search was conducted by A.K and A.S. Reference lists of recruited studies were checked to find additional relevant articles.

2.2. Inclusion and exclusion criteria

Titles, abstracts, and full texts of articles were read to find relevant studies and check eligibility criteria. Inclusion criteria were a) cross-sectional design; and b) assessing coinfection of candidiasis and pulmonary tuberculosis. Studies published before 2001, case reports, meeting reports, letters to editors, abstracts, case series, congress articles, editorials, literatures reporting inadequate data, articles published in languages other than English, duplicate publications, and narrative or meta-analysis/systematic reviews were excluded. Two reviewers (AK, AS) independently assessed the studies based on the inclusion and exclusion criteria. Disagreements on the inclusion or exclusion of studies were resolved by discussions between the two reviewers or by involving a third researcher.

2.3. Quality evaluation

Appraisal tool for Cross-Sectional Studies (AXIS) was used for assessing the quality of the included studies. Using this check, twenty items were evaluated in each study. If the related data was documented, a question was scored ‘yes’. In case of any doubt or indistinct data, a question was marked ‘no’ or ‘can’t tell’. According to the scoring system and the number of questions scored ‘yes’, the quality of studies was finally categorized as either ‘strong’, ‘intermediate’, or ‘weak’ [16]. Studies with weak quality were excluded (File 2).

2.4. Data extraction

The following data was extracted and tabulated: first author’s name, year of publication, location (country), sample size (TB⁺), rate of *Candida* coinfection, and detection method.

2.5. Statistical analysis

We used Comprehensive Meta-Analysis software (Version 3.3.070) for meta-analysis. Statistical significance level was considered as $P < 0.05$. Random effects model was used to calculate overall effects. Sources of between-study heterogeneity were assessed using Cochran’s Q and I square (I^2) tests and subgroup analysis. Egger’s regression asymmetry test was used to detect publication bias. The correlations between pulmonary candidiasis coinfection and patients’ characteristics such as age, gender, *body mass index* (BMI), and factors such as alcohol consumption, smoking, and diabetes mellitus (DM) were also scrutinized by Spearman correlation.

3. Results

3.1. Study selection

In total, 984 records were identified in primary literature search (Fig. 1). Of these, 453 duplicates were removed. Then abstracts and titles of 533 remained records were screened which resulted in exclusion of 401 irrelevant articles. Next, 130 full-text articles were assessed for eligibility criteria which led to the exclusion of 105 additional studies that did not fulfill inclusion criteria. After that, 25 studies were selected for qualitative appraisal. From these, seven studies with weak qualities were excluded. Finally, 18 studies entered quantitative synthesis (Meta-analysis).

3.2. Features of the selected studies

All the 18 included cross-sectional studies had been published between January 2001 and March 2019. The studies were from countries in Asia and Africa, especially from India with 9 reports. No report was from developed countries. Overall, 2139 TB positive patients were analyzed. The rate of candidiasis coinfection varied from 2.8% to 55%. Only phenotypic methods (i.e. AFB analysis-Direct Microscopy-Culture, Gram staining, KOH Mount, Ziehl-Neelsen technique, CHROM agar *Candida* culture method, Sugar fermentation tests, and Germ tube test) had been used to detect tuberculosis and fungal infections in all the studies. The studies’ characteristics have been described in Table 1.

3.3. Overall effects

The pooled prevalence of candidiasis coinfection among patients with pulmonary tuberculosis in Asia and Africa was 25.7% (95% CI: 23.7–27.9, $Q = 177.5$, $Z = 18.7$) (Table 2 and Fig. 2). The combined frequencies of candidiasis coinfections were 27.9% (95% CI: 21–36, $Q = 44$, $Z = 4.9$), 9.7% (95% CI: 1.3–46.8, $Q = 51$, $Z = 2$), and 30.7% (95% CI: 23.2–39.5, $Q = 4.6$, $Z = 4.1$) in India, Iran, and Nigeria respectively. No publication bias was detected by Funnel plot (Fig. 3) and

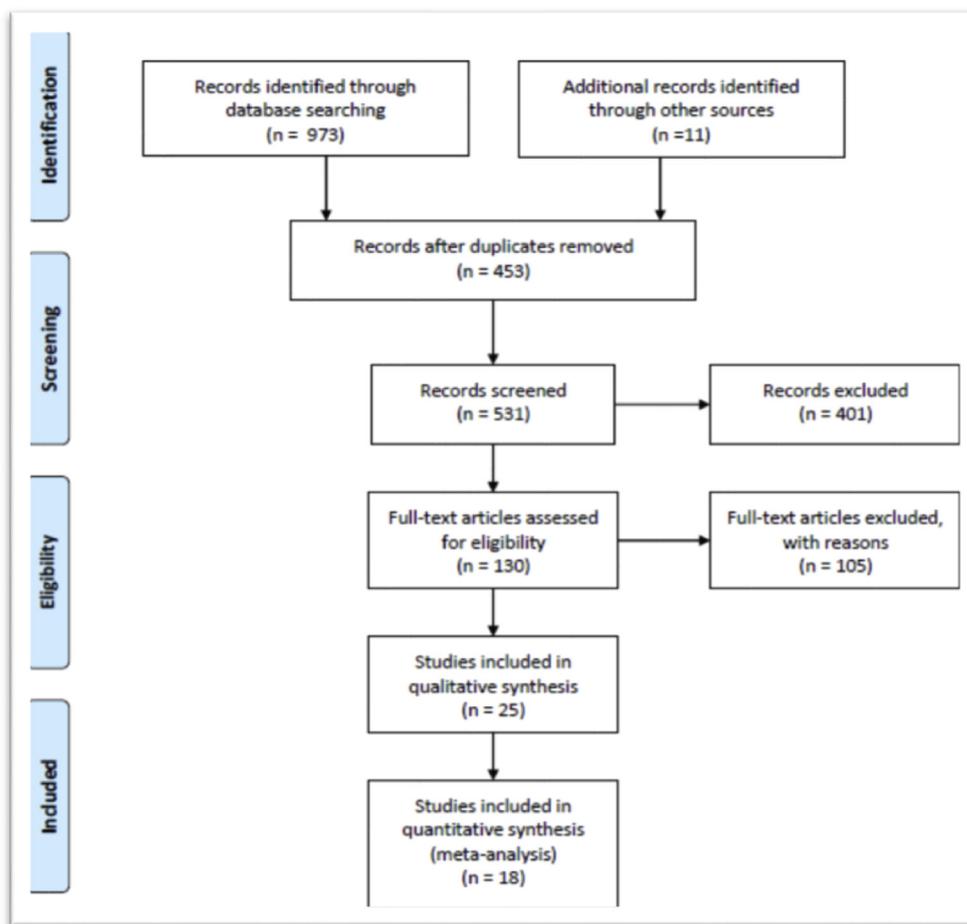


Fig. 1. Flow diagram of selection process of included studies.

Egger's linear regression ($P = 0.37$).

According to subgroup analysis, *C. albicans* was the most prevalent *Candida* spp. coinfecting patients with pulmonary tuberculosis (65.8%, 95% CI: 54.3–75.7, $Q = 47.6$, $Z = 2.6$). Also, the combined frequencies of *C. tropicalis* and *C. parapsilosis* were 16.9% (95% CI: 10.2–26.8), and 14.3% (95% CI: 7.1–26.7), respectively (Table 3).

3.4. Risk factors of candidiasis coinfection and its correlation with patients' demographic characteristics

A significant correlation was reported between advanced age and candidiasis coinfection in two studies ($p < 0.05$, Table 4). Also, three studies reported a significant correlation between male gender and candidiasis coinfection whereas only one study showed a correlation

Table 1
Characteristics of studies included in the present review.

Author	Time of Study	Publication(Year)	Location(Country)	Sample Size(TB +)	Candida- Coinfection	Detection Method	
						Molecular	Phenotypic ¹
Baradkar [2]	2006–2007	2009	India	100	26	-	+
Rathod [30]	2007–2008	2012	India	100	18	-	+
Kali [26]	2010–2011	2013	India	75	30	-	+
Mwaura [31]	2009	2013	Kenya	172	42	-	+
Mathavi [13]	2013	2014	India	107	21	-	+
Yahaya [32]	2013–2014	2014	Nigeria	28	11	-	+
Jabbari [33]	2014	2015	Iran	25	12	-	+
Yadu [34]	2006–2007	2015	India	100	30	-	+
Njunda [35]	2014	2015	Cameroon	44	20	-	+
Jabbari [36]	2006–2016	2016	Iran	430	12	-	+
Ndukwu [28]	-	2016	Nigeria	300	76	-	+
Babita [37]	2011–2012	2016	India	75	8	-	+
Astekar [38]	-	2016	India	60	33	-	+
Aldorkee [25]	2012–2014	2017	Iraq	100	8	-	+
Jabbari [3]	2007–2017	2018	Iran	130	6	-	+
Nandihal [24]	2012	2018	India	100	32	-	+
Hanson [39]	-	2019	Nigeria	93	32	-	+
Bin Najeeb [40]	2015	2019	India	100	29	-	+

Table 2
Pooled coinfection of *Candida* in pulmonary TB patients based on country.

Subgroups	Number of studies	Heterogeneity test			Egger's test		Random model		
		Prevalence (95% CI) (%)	Z	P	Q	P	I ²	T	P
Coinfection	18	25.7(23.7–27.9)	18.7	0.00	177.5	0.00	90.4	0.91	0.37
India	9	27.9(21–36)	4.9	0.00	44	0.00	81.8	1.2	0.25
Iran	3	9.7(1.3–46.8)	2	0.00	51	0.00	96	0.7	0.57
Cameroon	1	45.5(31.5–60.1)	0.6	0.54	0.00	1	0.00	-	-
Nigeria	3	30.7(23.2–39.5)	4.1	0.00	4.6	0.00	56.7	2.4	0.24
Kenya	1	24.4(18.6–31.4)	6.3	0.00	0.00	1	0.00	-	-
Iraq	1	8(4.1–15.2)	6.6	0.00	0.00	1	0.00	-	-

with female gender ($p < 0.05$). Alcohol consumption was not associated with candidiasis coinfection in neither of the studies ($p > 0.05$). One study reported low BMI as a potential risk factor for pulmonary candida coinfection, and two another studies described a correlation between candidiasis coinfection and smoking ($p < 0.05$). Finally, two studies reported higher prevalence of pulmonary fungal coinfection in tuberculosis patients with diabetes mellitus ($p < 0.05$).

4. Discussion

The rate of candidiasis coinfection varies from 2.8% to 55% in patients with pulmonary tuberculosis [17]. The present systematic review showed a combined prevalence of 25.7% for candidiasis coinfection in patients with pulmonary tuberculosis. The pooled frequencies of candidiasis coinfections were 27.9%, 9.7%, and 30.7% in India, Iran, and Nigeria respectively. The pooled prevalence of *Candida* coinfection was also obtained as 45.5% in Cameroon. Nevertheless, as estimations in Cameroon, Iraq, and Kenya were based on only one study, the reported frequencies may not indicate the true incidence of candidiasis coinfection in these countries. Therefore, it is recommended to perform more studies on this issue in the mentioned regions to more accurately

estimate the rate of coinfection. Variations in frequency of candidiasis and pulmonary tuberculosis coinfection are probably attributed to differences in the local prevalence of different candida species rather than different environmental conditions. Also, the types of clinical samples and detection methods can affect the reported rate of the coinfection [2].

Several studies have described candida species as the most common fungal agents retrieved from sputum of patients with pulmonary tuberculosis. Nonetheless, because of the presence of these fungi in throats of 30% of healthy individuals and risk of cross-contamination during sputum collection, the importance of candidiasis in tuberculosis patients has been undermined [18]. Kahanpaa et al. showed that *C. albicans* was the most common organism recovered from 60 to 70% of sputum samples, 16.5% of bronchial secretions, and 20.4% of lung fragments. *C. albicans* has also been isolated from 53.0% of healthy subjects' oral samples [19].

Similarly, *C. albicans* comprised the most prevalent fungus coinfecting patients with pulmonary tuberculosis followed by *C. tropicalis* and *C. parapsilosis* with respective frequencies of 65.8%, 16.9%, and 14.3%. In fact, all the studies included in present review reported *C. albicans* as the most common cause of fungal-tuberculosis coinfection.

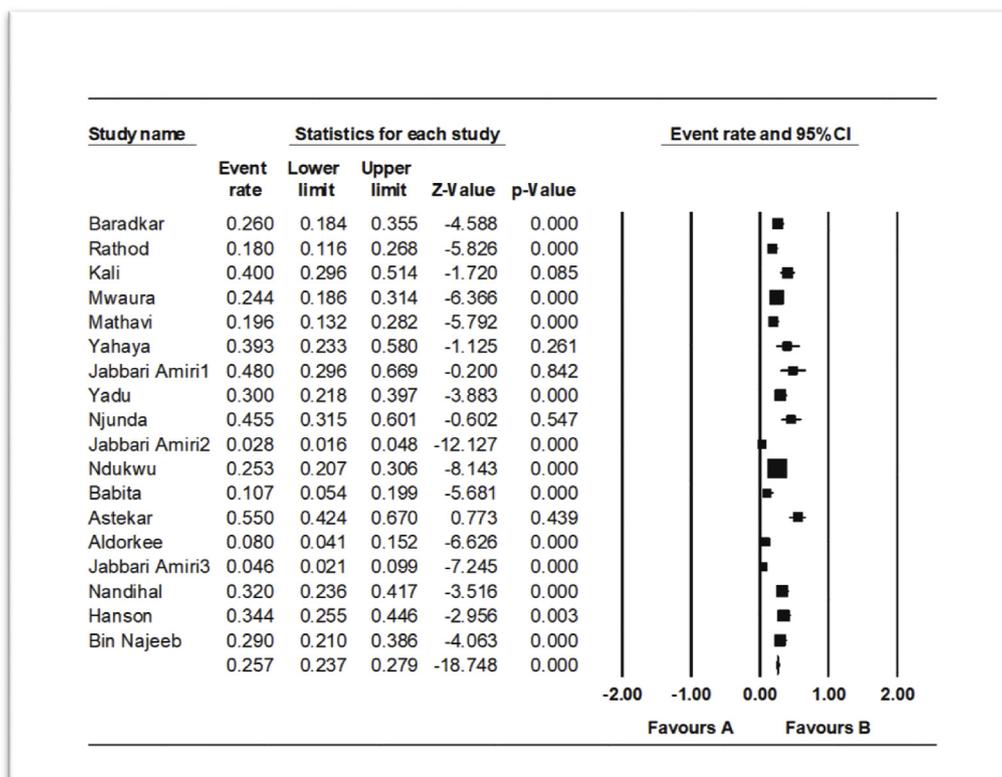


Fig. 2. The Forest plot of the meta-analysis of the prevalence of *Candida* coinfection among patients with pulmonary tuberculosis.

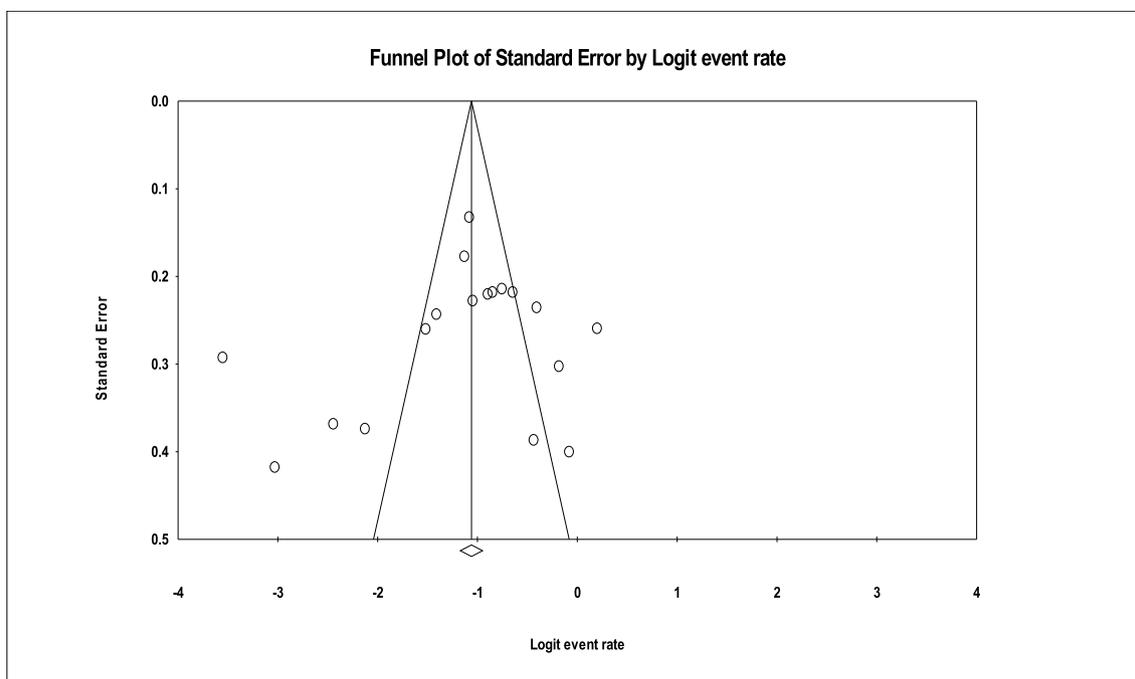


Fig. 3. Funnel plot of meta-analysis on the prevalence of Candida coinfection in patients suffering from pulmonary tuberculosis.

In line with our results, *C. tropicalis* has been noted as the second most prevalent cause of fungal coinfection in patients with tuberculosis. *C. tropicalis* is a new opportunistic pathogen representing higher rates of severe disease and deep tissue invasion than *C. albicans* in immunocompromised hosts [20,21]. According to our findings and results obtained by other studies, the high rate of coinfection with *C. albicans* and other *Candida* spp. may be due to cross-contamination or co-colonization and not necessarily reflect actual infection. For obviating this problem, it is recommended to use bronchoscopy rather than sputum sampling to reduce the risk of cross-contamination of samples with upper respiratory secretions. In practice; however, bronchoscopy is not always used in developing countries such as India and Cameroon [22].

Because of insufficient clinical data and unavailability of radiologic images, a high ratio of pulmonary fungal and tuberculosis coinfections reported in the analyzed studies may merely indicate colonization rather than actual infections. Nevertheless, clinical and radiological studies alone are inadequate to differentiate pulmonary fungal from

tuberculosis infections. Therefore, it is necessary to screen primary/secondary fungal infections using accurate detecting methods in patients with pulmonary tuberculosis [23]. This is of crucial importance considering that co-infections with opportunistic fungal and other non-tuberculosis pathogens can aggravate the clinical course of tuberculosis, accelerate disease recurrence, and increase mortality rate [10]. Nevertheless, no comprehensive epidemiological data is available about fungal coinfection as they frequently remain either misdiagnosed or undiagnosed. Except for Coccidioidomycosis, no fungal diseases have actually been reported to the Centers for Disease Control and Prevention (CDC) [10].

In the present review, three studies [3,24,25] showed a significant correlation between male gender and candidiasis coinfection ($p < 0.05$). On the other hand, only one study showed a correlation between female gender and candidiasis coinfection ($p < 0.05$) [26]. Our findings agreed with the reports of WHO indicating male gender as a predisposing factor for tuberculosis infection [27]. This may possibly

Table 3
Sub-groups analysis of Candida species.

Overall effects	Number of studies	Heterogeneity test			Egger's test		Random model		
		Prevalence (95% CI) (%)	Z	P	Q	P	I ²	T	P
<i>C. albicans</i>	15	65.8(54.3–75.7)	2.6	0.008	47.6	0.00	70.6	2.8	0.01
India	8	63.7(46.3–78.1)	1.53	0.21	27.2	0.00	74.3	3.7	0.009
Nigeria	2	57.4(47.9–66.4)	1.5	0.12	0.48	0.48	0.00	-	-
Iran	2	55.8(32.1–77)	0.46	0.84	1.7	0.19	41.4	-	-
<i>C. tropicalis</i>	8	16.9(10.2–26.8)	5.3	0.00	20.5	0.005	65.8	6	0.00
India	5	15.6(7.6–29.4)	4	0.00	10.1	0.003	60.5	5.6	0.01
Nigeria	2	24.8(11.4–45.7)	2.3	0.02	3.1	0.07	68.6	-	-
<i>C. parapsilosis</i>	7	14.3(7.1–26.7)	4.5	0.00	19.5	0.003	69.3	5	0.003
India	6	15.3(7.1–29.9)	3.8	0.00	17.3	0.004	71.1	4.7	0.009
<i>C. glabrata</i>	4	7.3(2.3–20.7)	1	0.00	6.3	0.09	53.1	10.4	0.009
India	4	7.3(2.3–20.7)	4.1	0.00	6.3	0.09	53.1	10.4	0.009
<i>C. krusei</i>	5	13.8(8.5–21.8)	6.5	0.00	3.8	0.42	0.00	2.4	0.09
India	3	13.9(7.9–24.8)	4.9	0.00	3.7	0.15	46.3	14.4	0.04
<i>C. dubliniensis</i>	3	6.2(2.8–13.1)	6.4	0.00	0.48	0.71	0.00	10.3	0.06
<i>C. guilliermondii</i>	2	4.9(1.6–14.1)	4.9	0.00	0.72	0.39	0.00	-	-

Table 4
The correlation between pulmonary candida coinfection with characteristics of patients and risk factors.

Author	Age(year)	Genus		Alcohol consumption	BMI	Smoking	DM
		Male	Female				
Baradkar	-	-	-	-	-	-	-
Rathod	-	-	-	-	-	-	-
Kali	47.77 ± 20.43	-	Higher(correlation) (P value = 0.01)	-	-	-	-
Mwaura1	adults	Higher(No-correlation)	-	-	-	-	-
Mathavi	-	Higher(No-correlation) (P value = 0.63)	-	Higher(No correlation) (P value = 0.72)	lower(correlation) (P value < .005)	Higher(correlation) (P value < .005)	-
Yahaya	-	-	-	-	-	-	-
Jabbari Amiri	-	-	-	-	-	-	-
Yadu	-	Higher(No-correlation)	-	-	-	-	-
Njunda	3–95	-	-	-	-	-	-
Jabbari	-	-	-	-	-	-	-
Ndukwu	-	Higher(correlation)	-	-	-	-	-
Babita	-	-	-	-	-	-	-
Astekar	20–80	Higher(No-correlation) (P = 0.22)	-	-	-	-	-
Aldorkee	22–65	Higher(correlation) (P values = 0.02)	-	-	-	Higher(correlation) (P values = 0.02)	Higher(correlation) (P values = 0.006)
Jabbari	0–80	Higher(correlation) (P = 0.01) (P value < 0.05)	-	-	-	-	-
Nandihal	-	Higher(correlation)	-	-	-	-	-
Hanson	-	-	Higher(No correlation) (P = 0.74).	-	-	-	-
Bin Najeeb	-	-	-	-	-	-	-

be related to higher environmental exposure of males than females to bacterial and fungal infections [28]. Nonetheless, Hidalgo et al. reported equal rates of *Candida* spp. colonization in both males and females [29]. Altogether, it is highly recommended to accurately identify all organisms recovered from clinical samples of patients with tuberculosis. The limitation of this study is that we only cite studies that existed in databases and other studies that were unpublished were not included in the study. We also did not contact to the authors of the articles in cases where further clarification was required.

In summary, the present review revealed high rate of candidiasis coinfection among patients with pulmonary tuberculosis. Considering that clinical and radiological evidences of fungal coinfections are unclear; accurate diagnostic procedures should be conducted to early diagnose and treat these opportunistic infections and decrease mortality and morbidity rates associated with fungal coinfection in tuberculosis patients.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.micpath.2019.103898>.

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