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

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ABSTRACT

Progress of the disease and prolonged treatment with antibiotics or immunosuppressive agents makes tuberculosis patients susceptible to fungal infections. This study aimed to determine the prevalence of pulmonary Aspergillus coinfection among patients with pulmonary tuberculosis in Asia and Africa.

The present review of cross-sectional studies was conducted on the prevalence of pulmonary Aspergillus coinfection among patients with pulmonary tuberculosis according to the PRISMA Protocol. Literatures published online in English from January 2001 to March 2019 via key databases such as Web of Science, MEDLINE, PubMed, Scopus, and Cochrane Library were searched. The used MeSH and non-MeSH keywords were; "pulmonary fungal", "pulmonary coinfection", OR "Pulmonary mycosis", "pulmonary fungal infections/agents", OR "Polymicrobial infection", OR "Secondary infection", OR "Mixed infections", "pulmonary aspergillosis", "fungi coinfection", "Fungal co-colonization", AND "pulmonary tuberculosis", OR "pulmonary TB", AND "Asia" AND "Africa". Finally, data analyzed using Comprehensive Meta-Analysis software (CMA).

The combined Aspergillus coinfection among patients with pulmonary tuberculosis was 15.4% (95% CI: 11.4–20.5), Q = 105.8 and Z = 9.57 in Asia and Africa. The most frequency of *Aspergillus spp.* was related to *A. fumigatus* with a combined prevalence of 57.6%. Most of the studies included in the present review showed a higher *Aspergillus* coinfection in the age group of 40 years and higher. Also, the existence of a correlation between increasing age and Aspergillus coinfection was reported ($p < 0.05$).

The present review showed a high combined Aspergillus coinfection among patients with pulmonary tuberculosis in Asia and Africa. Also, amongst the *Aspergillus spp.,* the most frequent was related to *A. fumigatus*.

1. Introduction

Progress of the disease and prolonged treatment with antibiotics or immunosuppressive agents makes tuberculosis patients immunocompromised and hence become susceptible to fungal infections [1]. When host defense is decreased, these unrecognized opportunistic fungi may affect the trend of disease or may even become fatal [2].

Coinfection is defined as the simultaneous presence of 2 or more infections, which may increase the severity and duration of one or both [3]. Pulmonary aspergillosis co-infection includes simultaneous infection of a host's lungs with *Aspergillus* spp., and *Mycobacterium tuberculosis* that cause more complications [4]. One cannot over-emphasize the point that the incidence and prevalence of respiratory fungal infections in many developing countries have remained largely unexplored and neglected. This has led to a widespread erroneous impression about their true public health importance [5]. Considering its devastating effects like other respiratory infections, this neglect has to be seen as a major call for concern. As reported by the Centers for Disease Control and Prevention (CDC), the mortality associated with Invasive Respiratory Aspergillosis (IRA) has increased by 35.7% since 1980 with the mortality of untreated IRA being nearly 100% [6]. On the other hand, the *Candida* also is the most commonly isolated fungal pathogen and may cause severe secondary infections in the immunocompromised population, including tuberculosis patients [1]. Also, acquired immune

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deficiency syndrome (AIDS) and immune deficiency are developing worldwide. Since opportunistic mycoses are a serious threat to such patients, it is anticipated that these infections may break out in epidemic proportions under suitable circumstances [7]. In comparison to HIV non-infected individuals, the human immunodeficiency viruses (HIV) infected individuals are more 10 times susceptible to developing tuberculosis (TB). Fungal pulmonary infections often precede the appearance of other opportunistic infections, but frequently co-exist with other pathogens [8]. Many physicians missed fungal pulmonary infection because it does not show specific clinical manifestations and usually hindered by other diseases like tuberculosis and cause high rates of morbidity and mortality. Therefore, there is a critical need for proper diagnosis of the opportunistic fungal pathogen especially in tuberculosis patients [9].

The main predisposing factor is the forming of a preexisting lung cavity secondary to tuberculosis [10]. A precondition for the pleural aspergillosis is the previously damage or destruction of lung or pleura through active tuberculosis [11]. *Aspergillus* species cause a serious pathologic condition (Aspergillosis) which is chiefly observed in immunocompromised people. Infection caused by *Aspergillus* can lead a wide spectrum of complications with radiological and pathologic features mimicking those of TB [12].

Studies are needed to define populations at high risk of these infections who might benefit from targeted antifungal and antibacterial chemoprophylaxis which remains the most promising of the potential preventive strategies [13]. Considering the importance of *Aspergillus* species and their coinfection with tuberculosis, and the lack of a comprehensive review in this regard, we performed a systematic review and meta-analysis to determine the *Aspergillus* coinfection among patients with pulmonary tuberculosis using summarizing data identified in the published literature.

2. Materials and methods

2.1. Search strategy

We conducted a systematic search for cross-sectional studies considered the Aspergillus coinfection among patients with pulmonary tuberculosis according to the PRISMA directions published from January 2001 to March 2019 and indexed in international electronic databases. Studies published online in the English language were selected from international databases (Google Scholar, PubMed, MEDLINE, Scopus, Cochrane Library, ScienceDirect, and Web of Science). The search was performed by AK and AS combining the following Medical subject headings (MeSH) and non-MeSH keywords; “pulmonary fungal”, “pulmonary coinfection”, OR “Pulmonary mycosis”, “pulmonary fungal infections/agents”, OR “Polymicrobial infection”, OR “Secondary infection”, OR “Mixed infections”, “pulmonary aspergillosis”, “fungi coinfection”, “Fungal co-colonization”, AND “pulmonary tuberculosis”, OR “pulmonary TB”, AND “Asia” AND “Africa”. We checked the reference list of retrieved relevant articles to find more studies.

2.1.1. Study eligibility criteria

The inclusion criteria were a) original studies with cross-sectional design; b) studies considered pulmonary *Aspergillus* coinfection with pulmonary tuberculosis. We included adults, children and other population other than HIV- infected people and cancer patients.

Also, studies that did not address this subject, articles published before 2001, commentaries, abstracts, case series, case reports, meeting reports, letters to editor, congress articles, editorials, literatures with illegibility in data reporting, articles reported in languages other than English, duplicate publication of the same article, review literatures, meta-analysis/systematic, and narrative reviews were excluded. Titles and abstracts of studies were reviewed independently by two reviewers (AK, AS) according to the eligibility criteria. Obvious discrepancies about the inclusion of studies were discussed with the third author (MHF).

2.2. Quality assessment

The quality of the studies included in the present review was evaluated by the criteria stated in Critical Appraisal Skills Programmed checklists (www.casp-UK). Several questions were designed for each study. If the relevant data was listed, the answer was scored as ‘yes’. If there was any doubt, or data was not defined in the study, that question was determined as ‘no’ or ‘can't tell’. studies categorized as ‘strong’, ‘intermediate’, or ‘weak’ according to the scoring system of the number of questions scored as ‘yes’ [14]. Finally, studies with weak quality excluded from the present review (File 1).

2.3. Data extraction

Two investigators (AK, AS) extracted the data {The first author's full name, Year of publication, Location (country), Sample size, Coinfection, Detection Methods (Molecular and Phenotypic)} from relevant studies. Furthermore, the extracted data were matched and inconsistencies between reviewers were discussed to reach an agreement.

2.4. Correlation between pulmonary Aspergillus coinfection and characteristics of participants and risk factors

The correlation between pulmonary Aspergillus coinfection and Characteristics of patients such as age and genus, also, risk factors including alcohol consumption, body mass index (BMI), smoking, and diabetes mellitus (DM) were investigated.

2.5. Statistical analysis

The random-effects model was used to calculate the crude prevalence and its corresponding 95% confidence interval (CI). Statistical heterogeneity between included studies was estimated using Cochran's Q test and I^2 statistic [15]. Substantial heterogeneity exists when I^2 exceeds 50% or p-value for the Cochran's Q test was < 0.05 [16]. We also used the subgroup analysis and Meta-regression to detect find possible sources of heterogeneity [17]. To detect the potential publication bias, Egger's regression asymmetry test was used; furthermore, the publication bias was checked using the funnel plot. The analyses were performed using comprehensive meta-analysis software (CMA) (Version 3.3.070). Two-tailed p values equal or less than 0.05 was considered as statistically significant.

3. Results

3.1. Study selection

Overall, 857 publications identified through online literature searching and manual searching, of which 324 were duplicates, abstracts, and titles of 533 articles were screened. Then, 360 were removed based on the abstracts and titles searching. Next, 173 studies included for full texts screening. Of these, 155 articles were excluded for the following reasons: case report, data missing, unclear data, no reporting coinfection, review studies, letters, meetings, studies in non-pulmonary tuberculosis cases, studies published other than English. Then, 18 articles included for qualitative assessment. A study excluded owing to poor quality. Finally, 17 studies included in the quantitative synthesis.

3.2. Characteristics of included studies

All the 17 selected studies were cross-sectional published between January 2001 and March 2019. All studies conducted in third world

Table 1
Characteristics of studies included in the present review.

Author	Time of Study	Publication (Year)	Location (Country)	Sample Size[a]	Coinfection(n)	Mean age	Gender (%)		Detection Methods	
							Male	female	Molecular	Phenotypic[1]
Shahid [30]	–	2001	India	20	5	46.3 + 12.4	–	–	–	+
Kurhadi [31]	–	2002	India	57	14	–	–	–	–	+
Bansod [32]	2002–2003	2008	India	1357	165	35	52	48	–	+
Njunda [7]	2010–2011	2012	Cameroon	27	9	36.5 ± 17.16	49.6	50.4	–	+
Osman [19]	–	2013	Egypt	50	12	45	72	28	+[2]	–
Mwaura [33]	2009	2013	Kenya	172	9	–	–	–	–	+
Jabbari Amiri [34]	2014	2015	Iran	25	10				–	+
Bhutia [35]	2013–2014	2015	India	14	2	50	59.5	40.5	–	+
Mathavi [21]	–	2015	India	107	17	–	–	–	–	+
Yadu [36]	2006–2007	2015	India	100	11	38.03	64	36	–	+
Njunda [37]	2014	2015	Cameroon	44	9	34	54.5	45.5	–	+
Jabbari amiri [38]	2006–2016	2016	Iran	430	16				–	+
Babita [39]	2011–2012	2016	India	75	10	–	–	–	–	+
Astekar [18]	–	2016	India	60	3	–			–	+
Aldorkee [40]	2012–2014	2017	Iraq	100	26	40.1 ± 10.8	65	35	–	+
Jabbari Amiri [29]	2007–2017	2018	Iran	130	10	48 ± 1.8	70	30	–	+
Bin Najeeb1 [41]	2015	2019	India	100	24	40 ± 10	73	27	–	+

[a] People who were positive for tuberculosis.

countries and developing countries, especially Asian populations. Of which, 9 from India, 3 from Iran, 2 from Cameroon, and remaining were from Kenya, Iraq, and Egypt. All studies had recruited both men and women, all precipitants (2868 people) were TB positive. All studies showed the *Aspergillus* coinfection in pulmonary tuberculosis patients. *Aspergillus* coinfection was varied between 3.7 and 33.3%. Sputum and BAL samples were used for diagnosis of TB. Blood, sputum, and BAL specimens were used for diagnosis of Aspergillus spp. Among studies, one used a molecular method for detection of tuberculosis and *Aspergillus* infections and remaining used of phenotypic methods. These methods were; AFB analysis-Direct microscopy-Culture, Gram stain, KOH Mount (KOH Preparation, Ziehl-Neelsen technique, Molecular Assay, Sugar fermentation tests, Molecular identification of sequenced ITS-18S rRNA genes, Microarray, ELISA, Dot Blot, and Agar gel diffusion. A summary of the study characteristics is provided in Table 1 (see Fig. 1).

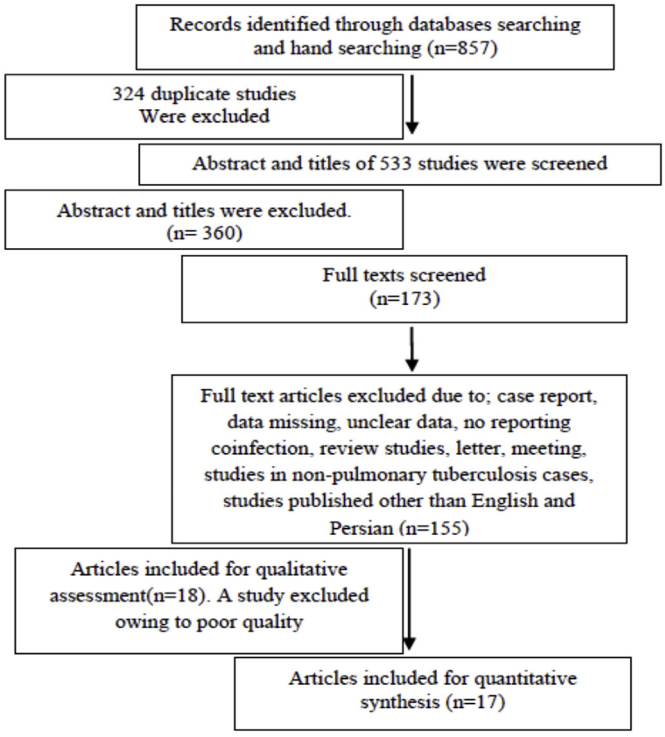

Fig. 1. Flow diagram of inclusion process of selected studies.

3.3. Overall effects

Table 2 and Fig. 2 show that the combined prevalence of *Aspergillus* coinfection among patients with pulmonary tuberculosis in Asia and Africa was 15.4% (95% CI: 11.4–20.5), Q = 105.8 and Z = 9.57, I^2 = 84.8. The combined prevalence of *Aspergillus* coinfection among patients with pulmonary tuberculosis in Asia was 14.7% (95% CI: 10.5–20.4), Q = 82.4 and Z = 8.78, I^2 = 85.4. The pooled prevalence of Aspergillus coinfection among patients with pulmonary tuberculosis in Africa was 17.7% (95% CI: 7.7–35.8), Q = 21.5 and Z = 3.16, I^2 = 86.

3.3.1. Overall effects of Aspergillus species

The most frequency of *Aspergillus spp.* was related to *A. fumigatus* with a combined prevalence of 57.6% (95% CI: 40.1–73.3), Q = 69.7 and Z = 0.84. Also, the combined prevalence of *Aspergillus flavus,* and *Aspergillus niger* were 27.2% (95% CI: 19.3–36.7), and 33.8% (95% CI: 28.8–39.3), respectively. Other information of Aspergillus spp. is abstracted in Table 3.

Table 2
Pooled Aspergilus coinfection in pulmonary TB patients based on location (continent).

Overall	Number of studies	Heterogeneity test			Egger's test		Random model		
		Prevalence (95% CI) (%)	Z	P	Q	P	I^2	T	P
Coinfection (Total)	17	15.4 (11.4–20.5)	9.57	0.000	105.8	0.00	84.8	0.8	0.4
Coinfection (Asia)	13	14.7 (10.5–20.4)	8.78	0.000	82.4	0.00	85.4	0.59	0.56
Coinfection (Africa)	4	17.7 (7.7–35.8)	3.16	0.002	21.5	0.000	86	0.79	0.50

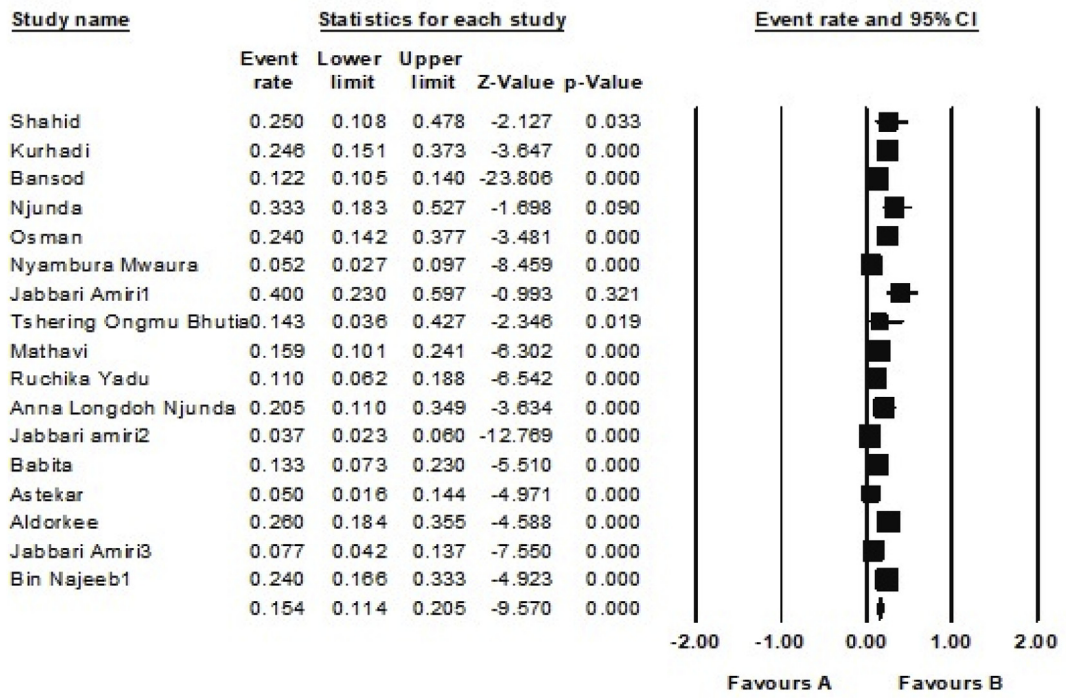

Fig. 2. The Forest plot of the meta-analysis of the prevalence of pulmonary Aspergillus coinfection among patients with pulmonary tuberculosis.

Table 3
Overall effects of Aspergillus species in included studies.

Aspergillus species									
Overall effects	Number of studies	Heterogeneity test			Egger's test		Random model		
		Prevalence (95% CI) (%)	Z	P	Q	P	I^2	T	P
Aspergillus flavus	11	27.2 (19.3–36.7)	4.3	0.00	17.5	0.00	42.9	0.19	0.84
India	4	19.2 (10.8–31.7)	4.2	0.00	3.7	0.00	20	5.2	0.03
Iran	3	51.8 (15–86.8)	0.07	0.93	7.2	0.00	72.3	0.71	0.61
Aspergillus fumigatus	14	57.6 (40.1–73.3)	0.84	0.39	69.7	0.00	81.3	0.55	0.58
Aspergillus fumigatus (in India)	7	62.7 (30.3–86.6)	0.75	0.45	59.7	0.00	89.9	0.52	0.61
Aspergillus fumigatus (in Iran)	2	49.3 (16.4–82.8)	0.03	0.97	3.4	0.00	71.3	–	–
Aspergillus niger	14	33.8 (28.8–39.3)	5.5	0.00	16.1	0.00	19.5	0.91	0.37
India	8	35 (29.3–41.2)	4.5	0.001	7.8	0.00	10.9	0.30	0.77
Iran	2	15.9 (6.1–35.7)	3	0.002	0.35	0.00	0.00	–	–

3.4. Sources of heterogeneity

Funnel plot did not show any publication bias (Fig. 3), also, the Egger's linear regression was used to further reveal publication bias. However, the results of Egger's linear regression revealed no publication bias ($P = 0.0$).

3.4.1. Specific subgroup analysis

To find possible sources of heterogeneity, subgroup analysis conducted based on location (Asia, and Africa) and gender (Male, and Female). The data abstracted in Fig. 4 didn't show strong evidence that location (Asia, and Africa) was associated with variation in the estimates. The heterogeneity was significant within groups (Q test = 103.9, $P = 0.00$); but between-study heterogeneity was not significant (Q test = 1.89, $P < 0.16$). Also, the heterogeneity was significant for male (Q test, $P = 0.00$, $I^2 = 82.2\%$); also, it was significant for female (Q test, $P = 0.00$, $I^2 = 82.6\%$) as well as for studies that reported the data for both genders together (Q test, $P = 0.00$, $I^2 = 89.1\%$). So, the heterogeneity was significant within groups (Q test = 91.1, $P = 0.00$); but between-study heterogeneity was not significant (Q test = 66.2, $P < 0.00$).

3.4.2. Meta-regression

Also, alongside with subgroup analysis, we conducted meta-regression to detect possible sources of heterogeneity. Meta-regression was performed for mean age. As reported in Fig. 5, there was strong evidence that mean age was associated with variation in the estimates. As it is clear from the slope of the line, as the slope increases (mean age) Aspergillus coinfection rate increases. Mean age could significantly explain the between-study heterogeneity $\beta = -0.06$, $P = 0.00$).

3.5. Findings of the correlation between pulmonary Aspergillus coinfection with characteristics of precipitants and risk factors

As reported in Table 4, most of the studies included in the present review showed the higher Aspergillus coinfection in the age group of 40 years and higher and the existence of a correlation between increasing age and Aspergillus coinfection ($p < 0.05$). Also, five studies showed the correlation between male genus and Aspergillus coinfection, whereas, only one study showed this correlation with the female genus

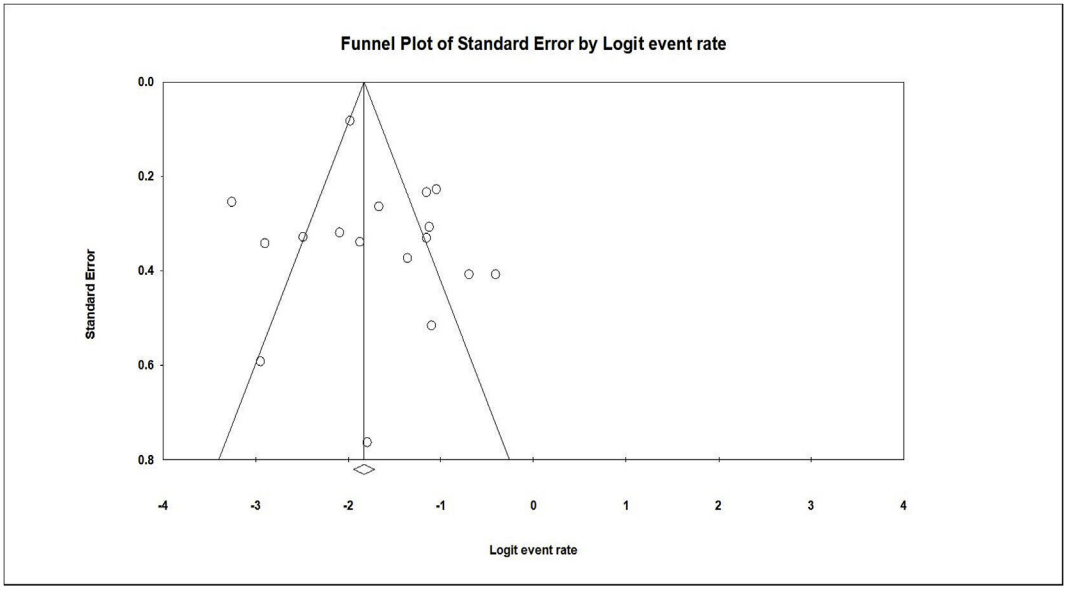

Fig. 3. Funnel plot of meta-analysis on the prevalence of pulmonary Aspergillus coinfection among patients with pulmonary tuberculosis.

($p < 0.05$). As well, no study reported the correlation between alcohol consumption and Aspergillus coinfection. A study showed a higher prevalence of pulmonary *Aspergillus* and Lower BMI. Also, three studies presented the correlation between Aspergillus coinfection and smoking ($p < 0.05$). Also, two studies reported the higher prevalence of pulmonary Aspergillus coinfection and diabetes mellitus (underlying disease).

4. Discussion

In the present study, *Aspergillus* coinfection was varied between 3.7 and 33.3%. As well as, the combined prevalence of Aspergillus coinfection among patients with pulmonary tuberculosis was 15.4%. The pooled prevalence of *Aspergillus* coinfection among patients with pulmonary tuberculosis in Asia was 14.7% versus the combined prevalence of Aspergillus coinfection in Africa (17.7%). Meat-regression results revealed that with increasing mean age, Aspergillus coinfection rate increased. Also, the most frequency of *Aspergillus spp.* was related to *A. fumigatus* with a combined prevalence of 57.6%. The combined *Aspergillus* coinfection reported from Kenya, Iraq, Nigeria, and Egypt only was extracted from one study. However, the combined *Aspergillus* coinfection of more than 15% was high, where this rate from Nigeria was 80% and from Iraq, and Cameroon was over than 25%. Interestingly, the pulmonary *Aspergillus* coinfection in Pulmonary TB^+ patients was reported by 5.2% from Kenya.

This difference in reporting *Aspergillus* coinfection in Pulmonary TB^+ patients between different countries predominantly attributed to the geographical location, health policies, climate conditions, and socio-economic condition, phenotypic, duration of anti-tuberculosis consumption by patients, clinical samples types, and molecular methods used for detection of *Aspergillus* infections in each country [18].

Most of the studies included in the present review showed the higher *Aspergillus* coinfection in the age group of 40 years and higher and the existence of a correlation between increasing age and *Aspergillus* coinfection. Also, 5 out of 17 studies showed a correlation

Groups		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared	
Group	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error
Fixed effect analysis												
Africa	4	0.169	0.125	0.224	-8.846	0.000	21.514	3	0.000	86.056	0.808	0.772
Asia	13	0.135	0.122	0.150	-30.192	0.000	82.413	12	0.000	85.439	0.393	0.271
Total within							103.927	15	0.000			
Total between							1.896	1	0.169			
Overall	17	0.138	0.125	0.153	-31.431	0.000	105.822	16	0.000	84.880	0.412	0.255

Groups		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared	
Group	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error
Fixed effect analysis												
Female	9	0.440	0.420	0.459	-5.952	0.000	46.029	8	0.000	82.620	0.096	0.076
Male	9	0.556	0.536	0.576	5.555	0.000	45.081	8	0.000	82.254	0.094	0.074
Total within							91.110	16	0.000			
Total between							66.204	1	0.000			
Overall	18	0.498	0.484	0.512	-0.276	0.783	157.314	17	0.000	89.194	0.141	0.084

Fig. 4. Pooled prevalence of Aspergilus coinfection in pulmonary TB patients based on subgroup analysis (location and gender).

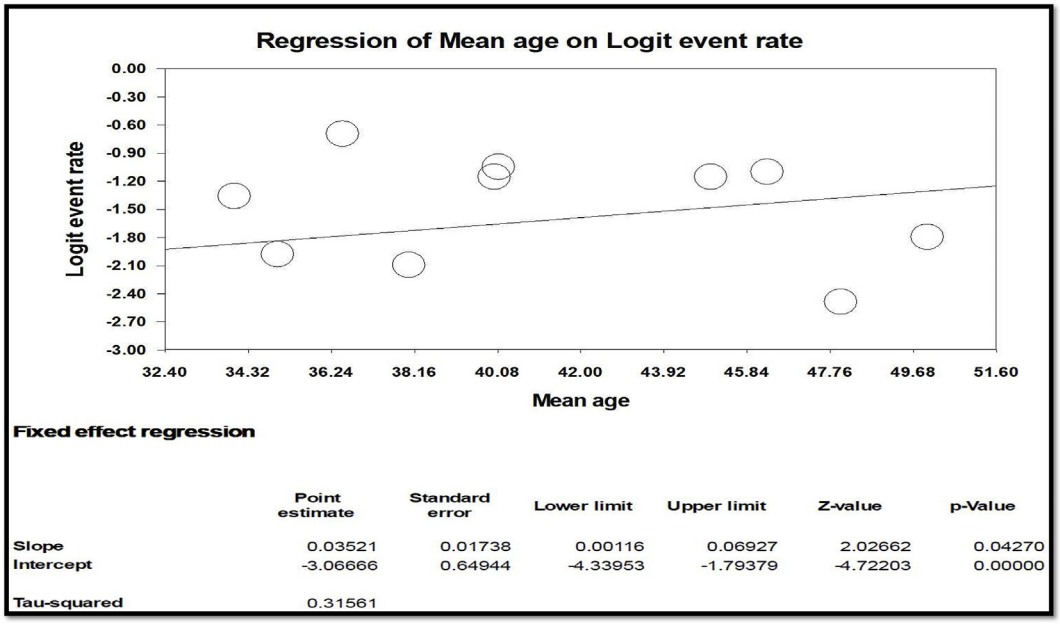

Fig. 5. Meta-regression of mean age on prevalence of pulmonary Aspergillus coinfection among patients with pulmonary tuberculosis.

between male genus and fungal coinfection, whereas, only one study showed this correlation with the female genus ($p < 0.05$). It is referred to this fact that the males are more vulnerable to infection than females due to their greater exposure to the surrounding [19]. As well, the aged patients over than 50 years, owing to the recurrent TB, the weakening of the immune system, and also the prolonged anti-tubercular therapy, becomes an effective predisposing factor for the beginning of coinfection by the fungal agents in active pulmonary tuberculosis [20].

Two studies conducted by Osman et al. [19], and Aldokree et al. included in the current review indicated a correlation between DM and fungal Aspergillus. Also, besides Osman and Aldokree, Mathavi et al. [21] showed a correlation between pulmonary Aspergillus coinfection and smoking. Similarly, Smoking and DM act as co-factors in quickening and increasing the immune-suppression mode [22,23]. The prevalence of mycotic infection in diabetic patients has been confirmed by Khanna et al. [24], they reported the main factors for prevalence of *Aspergillus* in pulmonary tuberculosis as following; the existence of resistant strains, the persistence of diseases, and underlying disease including diabetes mellitus.

To our knowledge, eight countries (India followed by, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa) account for two thirds of the total TB cases, the 30 high TB burden countries accounted for 87% of new TB cases [25]. Consequently, given the high rate of tuberculosis in high TB burden countries, the prevalence of Aspergillus coinfection is high. We showed that the most frequency of *Aspergillus spp.* was related to *A. fumigatus* with a combined prevalence of 57.6%. *A. fumigatus* can cause a variety of pulmonary diseases such as aspergilloma that characterised by saprophytic growth of the fungus in pre-existing tuberculous cavities [26]. Reports indicated a considerable worldwide burden of chronic pulmonary aspergillosis as a sequel to PTB [6]. In regions with a high occurrence of TB, criteria for the identification both CPA and tuberculosis are very identical that distinction between the two microorganisms is not possible, without serological tests for *Aspergillus*

Table 4
The correlation between pulmonary fungal coinfection with characteristics of precipitants and risk factors.

Author	Age (year)	Genus		Alcohol consumption	BMI	Smoking	DM
		Male	Female				
Shahid (2001)	45–65	–	1	–	–	–	–
Kurhadi (2002)	–	–	–	–	–	–	–
Bansod (2008)	35–44	Higher (correlation)	No	–	–	–	–
Njunda (2012)	61–70	No correlation	No correlation	–	–	–	–
Osman (2013)	No correlation	Higher (correlation)	–	–	–	Higher	Higher
Nyambura Mwaura (2013)	–	–	–	–	–	–	–
Jabbari Amiri (2015)	–	–	–	–	–	–	–
Bhutia (2015)	> 70	–	Higher	–	–	–	–
Mathavi (2015)	–	–	–	No	Low BMI(higher)	Higher	–
Yadu (2015)	50–59	-(64)	–	–	–	–	–
Njunda (2015)	41–50	no	no	–	–	–	–
Jabbari amiri (2016)	–	–	–	–	–	–	–
Babita (2016)	–	–	–	–	–	–	–
Astekar (2016)	–	–	–	–	–	–	–
Aldorkee (2017)	31–40	Higher	–	–	–	Higher	Higher
Jabbari Amiri (2018)	41–50	Higher (91)	Higher	–	–	–	–
Bin Najeeb (2019)	–	–	–	–	–	–	–

Note: The correlation related-data reported as narrative from studies included in the present review and no meta-analysis was done on them. DM: diabetes mellitus, BMI: body mass index.

antigens, even if the culture of samples (sputum, and etc) is positive for *A. fumigatus* [6].

Despite the completion of the course of treatment for tuberculosis by patients, secondary fungal infections had persistence of pulmonary symptoms. Therefore, suitable measures should be taken for patients in endemic areas for the potential of Co-infection and treated when clinically indicated to identify and treat these infections promptly [21]. It needs that all fungi detected in clinical specimens from patients especially immune-compromised and patients suffering from pulmonary tuberculosis should be carefully identified and physicians evaluate the clinical significance of these isolates in these patients [27]. Due to the importance of TB, should be paying more attention to the Co-infection of tuberculosis with opportunistic fungi. Because of comparable clinical signs of tuberculosis and pulmonary fungal Co-infection, in cases that direct smear and culture of samples for TB are negative, the specimens were evaluated for opportunistic fungi.

Notably, most of the included studies have used phenotypic methods to identify fungi except one case. Therefore, regarding the importance of pulmonary Aspergillus coinfection, the use of molecular methods and serological tests to identify *Aspergillus* coinfection is needed. On the other hand, mycosis infection if diagnosed early can be treated efficiently, and consequently can prevent from progress to fibrotic stage and avoided pulmonary disability [28]. Recognizing early chronic pulmonary aspergillosis (CPA) in patients with residual pulmonary shadows from pulmonary tuberculosis is only probable using microbiological testing (principally for *Aspergillus* IgG antibodies). If tests are not conducted, pulmonary mycoses can be easily misdiagnosed and mistreated as pulmonary tuberculosis, which leads to inappropriate therapy or none at all. In regions with a high occurrence of tuberculosis, due to the high similarity of CPA and pulmonary tuberculosis between them is not possible [6].

The limitations of this review are that, we only included the studies published in the electronic databases; therefore, unpublished data were missed from the present review. Second, this meta-analysis was performed on a limited number of articles (n = 17), which may limit statistical power for conducting a sufficient meta-analysis. Third, we couldn't conduct subgroup analysis and meta-regression due to insufficient data of Alcohol consumption, BMI, Participants (adults, children, and neonates), smoking, DM, and ect. These factors may have a significant effect on the variability of the estimates of prevalence. Finally, the correlation related-data reported as narrative from studies included in the present review and no meta-analysis was done owing to insufficient data, too.

In summary, the present review showed the high combined Aspergillus coinfection among patients with pulmonary tuberculosis in high burden countries including India in Asia and African countries. Also, amongst *Aspergillus spp.,* the most frequency was related to *A. fumigatus*. Thus, concerning the significance of pulmonary Aspergillus coinfection, the role of fungal agents in exacerbation of tuberculosis and the lack of improvement in tuberculosis symptoms such as chronic cough, sputum or occasional hemoptysis following completion of anti-tuberculosis chemotherapy, and miss diagnosis with tuberculosis, the use of molecular methods and serological tests to identify Aspergillus coinfection is necessary to early prevention from development to advanced fibrotic stage and avoided pulmonary disability [29]. Besides, this study suggested that Aspergillus-coinfection is a frequent event in patients who suffering from tuberculosis, so, the patients should be regularly checked for problems resulted from *Aspergillus*.

Declaration of competing interest

The authors declare that they have no competing interests.

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This study does not need to ethical approval because it is a review literature and ethical statement was not applicable.

References

[1] V.S. Rathod, J.S. Raut, S. Mohan Karuppayil, Antifungal drug susceptibility of Candida albicans isolates from pulmonary tuberculosis patients, Int. J. Pharm. Pharm. Sci., Suppl. 5 (2012) 323–326.
[2] V. Baradkar, M. Mathur, K. Wanjari, S. Kumar, Candida in pulmonary tuberculosis, Bombay Hosp. J. (2009) 52–53.
[3] T. Stedman, Medical Dictionary for the Health Professions and Nursing (P. 2339), Walters Kluwer Health. Lippincott Williams & Wilkins, 2012.
[4] S. Xerinda, N. Neves, L. Santos, A. Sarmento, Endotracheal tuberculosis and aspergillosis co-infection manifested as acute respiratory failure: a case report, Mycobact. Dis. 4 (2014) 2161-1068.1000160.
[5] H. Hagiya, Y. Kuroe, H. Nojima, J. Sugiyama, H. Naito, S. Hagioka, et al., Co-infection with invasive pulmonary aspergillosis and Pneumocystis jirovecii pneumonia after corticosteroid therapy, J. Infect. Chemother. 2 (2013) 342–347.
[6] D.W. Denning, A. Pleuvry, D.C. Cole, Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis, Bull. World Health Organ. (2011) 864–872.
[7] A.L. Njunda, A.A. Ewang, L.-H.F. Kamga, D.S. Nsagha, J.-C.N. Assob, D.A. Ndah, et al., Respiratory tract Aspergillosis in the sputum of patients suspected of tuberculosis in Fako division-Cameroon, J. Microbiol. Res. 4 (2012) 68–72.
[8] M. Rasheed, N. Thajuddin, Mycobacterial, bacterial and fungal pathogens causing pulmonary complications in patients with HIV infection, HIV & AIDS Rev. 1 (2011) 9–13.
[9] M. Pfaller, D. Diekema, Epidemiology of invasive candidiasis: a persistent public health problem, Clin. Microbiol. Rev. 1 (2007) 133–163.
[10] H. Ashna, A. Kaffash, A. Khaledi, K. Ghazvini, Mutations of rpob gene associated with rifampin resistance among Mycobacterium tuberculosis isolated in tuberculosis regional reference laboratory in northeast of Iran during 2015-2016, Ethiop. J. Health Sci. 3 (2018) 299–304.
[11] K.J. Ryan, C.G. Ray, Medical Microbiology, McGraw Hill, 2004, p. 370.
[12] T. Franquet, N.L. Müller, A. Oikonomou, J.D. Flint, Aspergillus infection of the airways: computed tomography and pathologic findings, J. Comput. Assist. Tomogr. 1 (2004) 10–16.
[13] Ogba O, Abia-Bassey L, Epoke J Prevalence Of Symptomatic Opportunistic Respiratory Mycoses And Mycobacterium Tuberculosis Among Human Immunodeficiency Virus Positive Patients In Calabar, Nigeria.
[14] CASP, 10 Questions to Help You Make Sense of Qualitative Research, (2006).
[15] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 11 (2002) 1539–1558.
[16] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, Bmj 7414 (2003) 557–560.
[17] M. Egger, G. Davey-Smith, D. Altman, Systematic Reviews in Health Care: Meta-Analysis in Context, John Wiley & Sons, 2008.
[18] M. Astekar, P.S. Bhatiya, G. Sowmya, Prevalence and characterization of opportunistic candidal infections among patients with pulmonary tuberculosis, J. Oral Maxillofac. Pathol.: JOMFP 2 (2016) 183.
[19] N.M. Osman, A.A. Gomaa, N.M. Sayed, Microarray detection of fungal infection in pulmonary tuberculosis, Egypt. J. Chest Dis. Tuberc. 1 (2013) 151–157.
[20] H. Randhawa, Respiratory and systemic mycoses: an overview, Indian J. Chest Dis. Allied Sci. 4 (2000) 207–219.
[21] S. Mathavi, R. Shankar, A. Kavitha, G. Sasikala, I. Priyadharsini, A study on prevalence of pulmonary candidiasis among tuberculosis patients and use of chromagar in identification of Candida species, J. Drug Deliv. Therapeut. 3 (2014) 118–121.
[22] C.Y. Jeon, M.B. Murray, Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies, PLoS Med. 7 (2008) e152.
[23] M.A. Baker, A.D. Harries, C.Y. Jeon, J.E. Hart, A. Kapur, K. Lönnroth, et al., The impact of diabetes on tuberculosis treatment outcomes: a systematic review, BMC Med. 1 (2011) 81.
[24] O. Ekenna, A. Uba, J. Chikwem, S. Mambula, M. Aliyu, I. Mohammed, Relevance of moldy fungi as agents of chronic lower respiratory tract infection in patients seen in Maiduguri, Nigeria, W. Afr. J. Med. 2 (2007) 117–120.
[25] J.F. Vesga, T.B. Hallett, M.J. Reid, K.S. Sachdeva, R. Rao, S. Khaparde, et al., Assessing tuberculosis control priorities in high-burden settings: a modelling approach, Lancet Glob. Health 5 (2019) e585–e595.
[26] R. Agarwal, G. Vishwanath, A.N. Aggarwal, M. Garg, D. Gupta, A. Chakrabarti, Itraconazole in chronic cavitary pulmonary aspergillosis: a randomised controlled trial and systematic review of literature, Mycoses 5 (2013) 559–570.
[27] M. Chadeganipour, S. Shadzi, P. Dehghan, J. Bijary, The incidence of opportunistic fungi in patients suspected of tuberculosis, Mycoses 7-8 (2000) 269–272.
[28] H.-S. Nam, K. Jeon, S.-W. Um, G.Y. Suh, M.P. Chung, H. Kim, et al., Clinical characteristics and treatment outcomes of chronic necrotizing pulmonary aspergillosis: a review of 43 cases, Int. J. Infect. Dis. 6 (2010) e479–e482.
[29] M.R.J. Amiri, R. Siami, A. Khaledi, Tuberculosis status and coinfection of pulmonary fungal infections in patients referred to reference laboratory of health Centers ghaemshahr city during 2007-2017, Ethiop. J. Health Sci. 6 (2018).
[30] M. Shahid, A. Malik, R. Bhargava, Prevalence of aspergillosis in chronic lung diseases, Indian J. Med. Microbiol. 4 (2001) 201.
[31] A. Kurhade, J. Deshmukh, R. Fule, C. Chande, S. Akulwar, Mycological and serological study of pulmonary aspergillosis in central India, Indian J. Med. Microbiol. 3 (2002) 141.
[32] S. Bansod, M. Rai, Emerging of mycotic infection in patients infected with

Mycobacterium tuberculosis, World J. Med. Sci. 2 (2008) 74–78.
[33] E. Mwaura, V. Matiru, C. Bii, Mycological findings of sputum samples from pulmonary tuberculosis patients attending TB clinic in nairobi, Kenya, Virol. Mycol. 2 (2013) 119, https://doi.org/10.4172/2161-0517.1000 119 Page 2 of 6 threatening diseases [12]. Candida.
[34] M.R. Jabbari, T. Shokohi, M. Abastabar, S.R. Aghili, M. Aliyali, G. Mohammadi, et al., Coexistence of opportunistic mycosis and mycobacterium tuberculosis in patients attending the Central Tuberculosis Reference Laboratory of Ghaemshahr city, Iran, Int. J. Mycobacteriol. 129 (2015).
[35] T. Buthia, L. Adhikari, Pulmonary mycoses among the clinically suspected cases of pulmonary tuberculosis, Int. J. Res. Med. Sci. 1 (2015) 260–268.
[36] M. Nawange, A. Kavishwar, Prevalence of opportunistic fungal infection in patients with pulmonary tuberculosis in Madhya Pradesh, Central India, J. Microbiol. Biomed. Res. 6 (2015).
[37] A.L. Njunda, D.S. Nsagha, J.C.N. Assob, B.W. Abange, A.J. Tamoh, T.E. Kwenti, Pulmonary paragonimiasis and aspergillosis in patients suspected of tuberculosis in yaounde, Cameroon, Br. Microbiol. Res. J. 4 (2015).
[38] S.R. Aghili, T. Shokohi, M.T. Hedayati, M. Abastabar, M. Aliyali, H. Hasanpour, Invasive forms of Candida and Aspergillus in sputum samples of pulmonary tuberculosis patients attending the tuberculosis reference laboratory in Ghaemshahr, Northern Iran: an analysis of samples collected during the past 10 years, Int. J. Mycobacteriol. 5 (2016) S179–S180.
[39] S.S. Babita, K. Prabhat, Prevalence of mycotic flora with pulmonary tuberculosis patient in a tertiary care hospital, Int. J. Contemp. Med. Res. 9 (2016) 2563–2564.
[40] Suad Yousuf Aldorkee MFAj, Prevalence of opportunistic fungal infection in pulmonary tuberculous patients, J. Babylon Univ./Pure Appl. Sci. 3 (2017) 968–974.
[41] M.A.B. Najeeb, B.N. Mahantesh, Prevalence of fungi as opportunistic pathogens in active and post-treated pulmonary tuberculosis cases-A comparative study, EC Microbiol. (2019) 153–157.