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REVIEW

Bacterial infections in acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis

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Abstract

Objective Due to the importance of Chronic obstructive pulmonary disease (COPD) as the fourth cause of mortality worldwide and the lack of studies evaluating the prevalence of bacterial infections in disease exacerbation, this systematic review and meta-analysis was performed to determine the prevalence rate of bacterial infections in COPD patients.

Methods PubMed, ISI Web of Science, and Scopus databases were systematically searched for population-based prevalence studies (1980–2018). MeSH terms for "Bacterial infections" and "AECOPD" were used as search keywords. The selected studies were filtered according to the inclusion and exclusion criteria. Fixed and random-effects models were used for estimation of summary effect sizes. Between-study heterogeneity, as well as publication bias, were calculated.

Results Finally, 118 out of 31,440 studies were selected. The overall estimation of the prevalence of bacterial infection was 49.59% [95% confidence interval (CI) 0.4418–0.55]. The heterogeneity in estimating the pooled prevalence of bacterial infections was shown in the studies (Cochran Q test: 6615, $P < 0.0001$, $I^2 = 98.23\%$). In addition, *S. pneumoniae, H. influenzae, M. catarrhalis, A. baumannii, P. aeruginosa, and S. aureus* were the most prevalent reported bacteria.

Conclusions Our results as the first meta-analysis for the issue demonstrated that bacterial infections are an important risk factor for AECOPD. Further studies must be performed for understanding the exact role of bacterial agents in AECOPD and help physicians for more applicable preventive and therapeutic measurements.

Keywords AECOPD · Bacterial infections · Meta-analysis · Systematic review

Introduction and objectives

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent type of obstructive lung disease involved ~ 174 million people worldwide [132]. The main clinical symptoms of COPD include cough, shortness of breath, and sputum production [19], with periods of acute exacerbations (AECOPD) that characterizes by increased cough, more shortness of breath, sputum color changing, and increase in sputum production [11, 19]. Among several risk factors suggested to play role in COPD/AECOPD pathogenesis, respiratory bacterial infections are correlated with approximately 50% of cases [11], as studies have demonstrated a significant correlation between the lower airway bacterial load and COPD consequences [86, 118]. Accordingly, many experimental and review studies have reported a wide range of bacterial species involved in COPD/AECOPD patients, among which respiratory microbiome is a key player [28, 104]. Due to demographic and geographical variations, different clinical specimens, and various detection methods (including molecular methods such as PCR and RT-PCR and serology), different bacterial species have been isolated from the patients. Since there are few studies tried to pool and meta-analyze these heterogeneous studies altogether, the prevalence and geographical distribution of respiratory bacterial infection in AECOPD has not yet been clearly defined. In the previous study, a systematic review and meta-analysis was performed by the present authors on 28 studies selected

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out of 26,078 articles to determine the prevalence of viral infections in AECOPD, resulting in the about 43% overall viral prevalence rate [52]. To the best of our knowledge, there is no systematic review and meta-analysis on the prevalence of bacterial infections in AECOPD. Accordingly, in the present study, we aimed to determine the frequency of bacterial infections in COPD/AECOPD patients through a systematic review and meta-analysis study.

Data source and study selection

Search strategy

A systematic search was performed in the main databases, including PubMed, Scopus, and ISI Web of Science to identify available articles to May 2018. According to MeSH terms, searches were performed using the following keywords: "chronic obstructive pulmonary disease", "COPD", "Exacerbation", "infection", "microbe", "bacteria", and "colonization", alone or combined together with the Boolean operators "OR", "AND", and "NOT" in the Keywords/Title/Abstract fields. In addition, the reference list of selected full-text papers was precisely searched manually to find additional citations not retrieved in the first step of the systematic search. Gray literature, dissertations, and relevant proceedings of international congresses were not explored. Finally, we restricted our search to the original articles or abstracts published which reported the prevalence of bacterial infections in COPD patients. The literature search was conducted by two independent researchers in two stages. Disagreements among researchers were resolved by discussion or, if necessary, by a third researcher. Journals and authors were not blinded during study selection.

Inclusion and exclusion criteria

A protocol for inclusion and exclusion criteria was defined for eligible peer-reviewed publications according to the following inclusion criteria: (A) Articles published up to May 2018, (B) The articles in English language reporting the prevalence of bacterial infections in COPD patients, (C) All studies included samples from sputum, nasopharyngeal swab, bronchoalveolar lavage, brushing, and nasal lavage, and (D) reported data related to a group of individuals taken from the general population. The main exclusion criteria were: (A) Studies with unknown sample origins, (B) Studies that failed to present data clearly, (C) Studies conducted on animal models, (D) Studies with overlapping subjects, time, and place of sample collection, and (F) Congress abstracts, review articles, case report articles, meta-analysis or systematic reviews, and duplicate publication of the same study.

Quality assessment and data extraction

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines were used to assess the quality of the included studies by two researchers, independently. The PRISMA statement consists of a 27-item checklist and four-phase flow diagram [75]. A complete information list was extracted from the articles into a Microsoft Excel worksheet. These data were included the first author's name, publication date, sample size, the prevalence of bacterial infection, Age mean, detection method, biological sample, smoking status, risk factors, and reference. Furthermore, unclear data were consulted and achieved consensus before recording an entry in the dataset. Cohen's κ was acceptable between the researchers as the agreement coefficient and was considered equal to 0.80.

Statistical methods

Pooled relative frequency (RF) and its corresponding 95% CI were used to evaluate the prevalence of bacterial infections in COPD. The heterogeneity and the variation in the pooled estimations were assessed using Cochran's Q test and I2 index, respectively, and was considered significant at $P < 0.05$ level [71]. The pooled RF was calculated by a random effect model while significantly heterogeneity existed between the individual studies, and otherwise, this pooled effect sizes were derived from a fixed-effect model. A funnel plot was established for checking the existence of publication bias. The funnel plot asymmetry was measured by Egger's linear regression test and Begg's test ($P < 0.05$ levels were considered statistically significant for publication bias) [51]. Finally, the subgroup analysis was used in the year of publication, age average, biological sample, detection method, smoking status, and risk factors. All statistical analyses were conducted by data analysis and statistical software (STATA) (version 11.0; Stata Corporation, College Station, TX) and MedCalc software.

Results

Literature review

The study selection process and the flowchart of the literature search are shown in Fig. 1. Through our search in PubMed, Scopus, and ISI web of science database and references, 31,440 articles were identified for "Exacerbation" in the title or abstract. In primary screening, 29,679 publications were excluded according to COPD Mesh terms in the title or abstract (COPD, chronic obstructive pulmonary

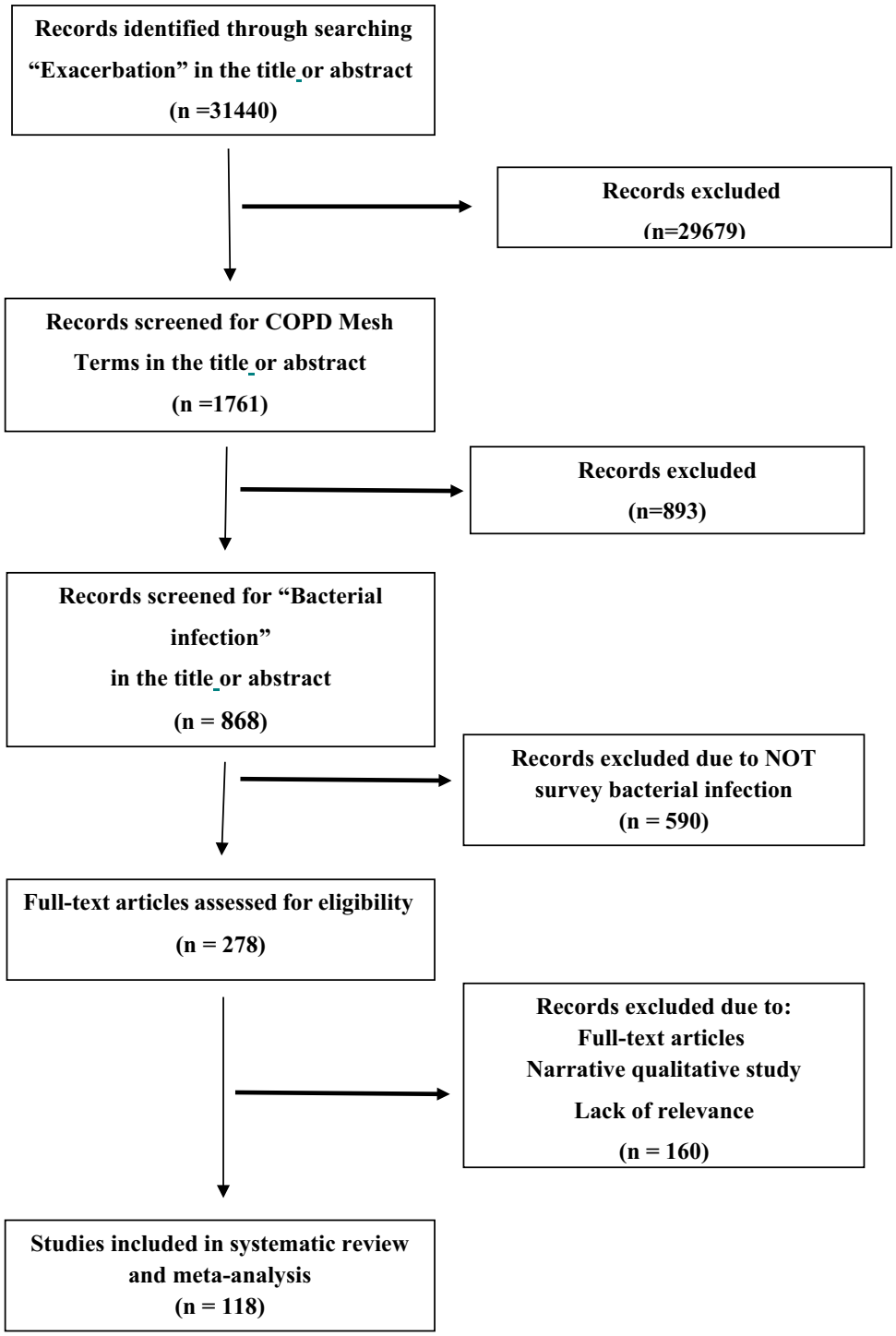

Fig. 1 Flowchart of the systematic search and the resulted number of final selected studies

disease). The retained publications were screened according to "Infection" Mesh terms, including "Infect*" OR "Microb*" OR "Bacteria" OR "Bacterium" OR "Colonization" in the title and abstract that resulted in 868 publications. Then, after manually assessing for bacterial infections in the title and abstract and eligibility evaluation, finally, 118 papers were retained for full-text evaluation. Two independent researchers did the literature search in two stages. Disagreements among researchers were resolved by discussion or, if necessary, by a third researcher. Journals and authors were not blinded during study selection.

Study characteristics

Out of all studies entered into the meta-analysis, 32 studies (27%) were published before 2005 and others (73%) were after

2005. Most studies were conducted in Spain (14.4%) and only less than 1% were published in England and Japan (Table 1).

Overall prevalence

According to included studies, the pooled estimation for the prevalence of bacterial infection in COPD patients was 0.4959 (95% CI 0.4418–0.55). Total patients analyzed for the pooled prevalence of bacterial infection were 19,409 among which, 8447 cases were positive for bacterial infections. The most common isolated pathogens were including *H. influenzae, S. pneumoniae, Klebsiella pneumoniae, S. aureus, M. catarrhalis, A. baumannii,* and *P. aeruginosa*. The heterogeneity for estimating the pooled prevalence among the studies was shown; Cochran *Q* test: 6615, $P < 0.0001$, $I^2 = 98.23\%$ (Fig. 2 and Table 2).

Subgroup analysis

As we analyzed for the time trend of bacterial infections in AECOPD, the LOWESS Smoother plot showed a significant shift in bacterial infections prevalence in 2005. In fact, subsequent to a decreasing rate of bacterial prevalence in AECOPD studies, an increasing shift is seen after 2005 and continues almost steadily. Therefore, it seems that bacterial infection was noted to be more prevalent in studies published after 2005 (0.4939; 95% CI 0.4281–0.5598). As shown in Fig. 3, culture is constantly used in most studies but a dramatic shift was seen in applying PCR-based methods for detecting bacterial infections in AECOPD. More than 60 years old was the most common group of patients (0.5114; 95% CI 0.446–0.5767, $P < 0.001$). Sputum was the most used clinical specimen (82.2%) (0.4943; 95% CI 0.4328–0.5558, $P < 0.001$) and culture was the most common detection method (83.8%) (0.4956; 95% CI 0.4375–0.5538, $P < 0.001$). More information on Subgroup analysis is presented in Table 2. In addition, the prevalence of bacterial infection in COPD patients increased over age and decreased in men, approximately (Fig. 4).

Publication bias

Although publication bias was statistically significant in some cases based on Egger's regression test, no publication bias was detected according to the Begg's adjusted rank correlation test (Table 2 and Fig. 5).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis about the prevalence of bacterial infections in AECOPD patients, showing that the prevalence of bacterial infections is 49.5% (95% CI 0.4418–0.55). Although about 20% of the AECOPD cases may be a co-infection of simultaneous bacterial and viral infections, according to the principal objective of our study, we determined only the role of bacterial infections in AECOPD patients. The majority of the most common microorganisms, including *S. pneumoniae*, *H. influenza*, and *M. catarrhalis,* were a part of the respiratory microbiome. It seems reasonable, since microbiome dysbiosis is a major cause of chronic respiratory complications that can disturb homeostasis in the lung resulting in lung inflammation and infection [104]. Sethi et al. isolated bacterial agents from sputum samples of 40–60% of COPD patients [107]. A study in 2003 identified bacterial infections in 43.3% of AECOPD patients as the major risk factor with the dominance of *H. influenzae* (13.3%) [76]. Several other studies have isolated *H. influenzae, Streptococcus pneumoniae, Moraxella catarrhalis*, and *Pseudomonas* as the most common bacteria from both stable and exacerbated COPD [11, 37, 72]. In most studies, the average age of patients was above 60 years. Previous studies have shown that young age groups of COPD patients may be more likely to show worse clinical outcomes [48]. Another influencing factor is the bacterial detection method. As shown in the subgroup analysis for the year of publication, after a decreasing rate of bacterial prevalence in AECOPD studies, an increasing shift is seen after 2005. This shift may be due to three possible reasons: first, molecular techniques (with higher sensitivity and being independent of previous antibiotic administration) are mainly introduced almost after 2005; second, bacterial culture systems have been progressed more frequently; and third, it is simply due to the slight changes in the prevalence of bacterial caused AECOPD before and after 2005. In this meta-analysis, the most common detection method was the culture (83.8%) (0.4956; 95% CI 0.4375–0.5538, $P < 0.001$). For bacterial detection, culture is the gold standard method, but has some shortcomings such as time-consuming and low sensitivity [38, 61]. Despite being expensive and more complicated, molecular techniques have several advantages including higher sensitivity, being able to detect noncultivable bacteria, being independent of previous antibiotic administration, and can quantitatively determine the load of bacteria [38]. In addition, since it is proved that changing in the total pattern of microbiome content is the cause of asthma and COPD rather than changing in an individual bacterial species, next-generation sequencing techniques would be needed to give a comparison between healthy and patients respiratory microbiome. We found ELISA as the third most common method in 21 studies (0.5099; 95% CI 0.3767–0.6423, $P < 0.001$), as a fast but low specific method. In fact, sandwich and indirect ELISA methods used to evaluate microbial antigens and/or antibodies are

Table 1 Characteristics of studies included in the systematic review and meta-analysis

Location	No. of samples	Bacterial species	Method	Type of sample	References
Australia	120	*M. catarrhalis*	Culture, ELISA	Serum, Sputum	[1]
	38	*H. influenzae, M. catarrhalis, S. pneumoniae, P. aeruginosa*	Culture	Sputum	[124]
	59	*H. influenzae, S. pneumoniae, M. catarrhalis*	Culture, Real-time PCR	Sputum	[117]
	27	*H. Influenzae*	ELISA, PCR	Blood, BA	[121]
Bangladesh	90	*Acinetobacter, Enterobacter, M. catarrhalis, Pseudomonas spp., Klebsiella, S. pneumoniae, H. influenzae*	Culture	Sputum	[8]
	60	*Klebsiella pneumoniae, S. aureus, S. pneumoniae, P. aeruginosa*	Culture	Sputum	[99]
Bosnia and Herzegovina	75	*S. pneumoniae, Klebsiella pneumoniae, E. coli, A. baumannii, Enterobacter cloacae, S. aureus, P. aeruginosa, Enterobacter freundii, Proteus mirabilis, H. influenzae, Klebsiella oxytoxica*	Culture	Sputum	[27]
Canada	56	*H. Influenzae, S. pneumoniae*	PCR	Sputum	[63]
China	30	*S. aureus, S. pneumoniae, H. influenzae, M. catarrhalis, P. aeruginosa, S. epidermis, Micrococcus* spp.	Culture	BA	[134]
	61	*Chlamydophila pneumoniae*	PCR, MIF	Sputum, Blood	[34]
	45	Not available	Culture	Sputum	[20]
	70	*H. influenzae, H. parainfluenza, S. pneumoniae, M. catarrhalis, S. aureus, P. aeruginosa, Klebsiella pneumonia, A. baumannii*	Culture	Sputum, Blood	[21]
	130	*H. parainfluenzae, S. pneumoniae, H. influenzae*	Culture	Sputum	[135]
	586	*P. aeruginosa, E. coli, Klebsiella pneumoniae, S. aureus, A. baumannii, H. influenzae*	Culture	Sputum	[59]
	81	*P. aeruginosa, Klebsiella pneumoniae, Enterobacter cloacae, A. baumannii, E. coli, S. maltophilia, H. influenza*	Culture, CRP assay	Sputum, Blood	[94]
	884	*P. aeruginosa, Klebsiella pneumoniae, H. influenzae, S. pneumoniae, H. parainfluenzae, A. baumannii, M. catarrhalis, E. coli*	Culture	Sputum	[133]
	172	*Enterobacteriaceae*	Culture	Sputum	[46]
	6	*Acinetobacter, Prevotella, Neisseria, Rothia, Lactobacillus, Leptotrichia, Streptococcus, Veillonella, Actinomyces.*	Microarray	Sputum	[122]
	135	*H. influenzae, P. aeruginosa, S. pneumoniae, Klebsiella pneumoniae, M. catarrhalis, Stenotrophomonas maltophilia, Enterobacter cloacae, Serratia marcescens, A. baumannii, E. coli*	Culture	Sputum, Blood	[22]
	81	*P. aeruginosa, A. baumannii, Klebsiella, E. coli, S. pneumonia*	Culture	Sputum	[29]
	318	*Klebsiella. pneumoniae, P. aeruginosa, A. baumannii, S. pneumoniae, S. aureus*	Culture	Sputum	[125]
	710	*P. aeruginosa, E. coli, A. baumannii, Klebsiella pneumoniae, S. aureus, S. pneumoniae, S. epidermidis, Enterococcus, Enterobacter cloacae*	Culture	Sputum	[24]
Czech Republic	90	*S. milleri group*	Culture, PCR	Sputum, NS	[82]
Denmark	118	*H. influenzae, S. pneumoniae, M. catarrhalis, P. aeruginosa*	Culture	Sputum	[60]

Table 1 (continued)

Location	No. of samples	Bacterial species	Method	Type of sample	References
Egypt	376	*S. pneumoniae, Chlamydophila pneumoniae, Klebsiella pneumoniae, H. influenzae, M. catarrhalis*	Culture, MIF	Blood, Sputum	[2]
	30	*S. pneumoniae, S. aureus, Haemophilus influenzae, Acinetobacter spp., M. catarrhalis*	Culture	Sputum	[35]
England	120	*H. influenzae, M. catarrhalis, S. pneumoniae*	Real-time PCR	Sputum	[9]
Finland	90	*Chlamydophila pneumoniae*	MIF	Blood	[130]
France	35	*H. influenzae, S. pneumoniae, P. aeruginosa, M. pneumonia*	Culture, Cytology, ELISA	Nares	[96]
	857	*S. pneumoniae, H. influenzae, P. aeruginosa, A. baumannii, Stenotrophomonas maltophilia*	Culture	TA	[85]
	200	*H. influenzae, S. pneumoniae, M. catarrhalis, Pseudomonas spp., E. coli, Serratia marcescens, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter cloacae, A. baumannii*	Culture	Sputum	[101]
	98	*H. influenzae, S. pneumoniae, methicillin-sensitive S. aureus*	Culture	Tracheal Aspirate	[84]
	51	*H. influenzae, M. catarrhalis, S. pneumoniae, P. multocida, Proteus vulgaris, H. parainfluenzae*	Culture, PCR, Microarray	Sputum	[95]
Germany	112	*S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis, P. aeruginosa, Serratia marcescens, Klebsiella pneumoniae, Proteus vulgaris, E. coli, Citrobacter spp., Enterobacter spp., Stenotrophomonas maltophilia*	Culture	Sputum	[36]
	193	*S. pneumoniae,, H. influenzae, P. aeruginosa*	Culture	Sputum	[67]
	57	*E. coli, H. haemolyticus, H. influenzae, M. catarrhalis*	Culture	Sputum, Urine, Blood	[100]
Greece	75	*Chlamydophila pneumoniae*	Culture, ELISA, MIF	Sputum, Blood	[88]
	100	*Mycoplasma pneumoniae*	Culture, ELISA	Sputum, Serum	[87]
	92	*H. influenzae, P. aeruginosa, A. baumannii, C. pneumoniae, M. pneumoniae*	Culture, PCR, ELISA	Sputum, Serum	[80]
India	100	*Mycoplasma pneumoniae*	Culture, PCR, ELISA	Sputum, Throat Swab	[129]
	377	*M. catarrhalis*	Culture	Sputum	[26]
	148	*H. influenza, S. pneumoniae, P. aeruginosa, Klebsiella Pneumoniae, S. aureus*	Culture	Sputum	[4]
	200	*Klebsiella pneumoniae, P. aeruginosa, S. aureus, S. pneumoniae, E. coli*	Culture	Sputum	[106]
	50	*H. pylori*	ELISA	Blood	[131]
	100	*S. pneumoniae, P. aeruginosa, Klebsiella, Citrobacter, gram-negative nonfermenting bacteria, E. coli*	Culture	Sputum	[115]
	477	*S. pneumoniae, P. aeruginosa, M. catarrhalis, H. influenzae, Klebsiella pneumoniae, Stenotrophomonas maltophilia, A. baumannii, S. aureus, Group C Streptococci*	Culture	Sputum	[123]
	160	*Acinetobacter, Klebsiella pneumoniae, Klebsiella oxytoca, P. aeruginosa, E. coli, S. pneumoniae*	Culture	Sputum	[114]

Table 1 (continued)

Location	No. of samples	Bacterial species	Method	Type of sample	References
	100	*K. oxytoca, Klebsiella spp., Klebsiella pneumoniae, E. coli, Acinetobacter, C. freundii, P. aeruginosa, S. pyogenes, S. aureus*	Culture	Sputum	[81]
	72	*P. aeruginosa, Klebsiella pneumoniae, S. aureus, S. pneumoniae, Acinetobacter spp.*	Culture	Sputum	[58]
Iran	90	*Bordetella pertussis*	ELISA	Blood	[47]
Israel	4	*Chlamydophila trachomatis*	MIF	Blood	[92]
	240	*Legionella spp., M. pneumoniae, Coxiella burnetii, S. pneumoniae, H. influenzae, M. catarrhalis*	Culture, MIF	Blood, Sputum	[64]
	219	*Chlamydophila pneumoniae*	MIF	Blood	[64]
	240	*Legionella pneumophila*	MIF	Blood	[65]
	240	*Mycoplasma pneumoniae*	ELISA	Blood	[66]
	190	*Simkania negevensis*	ELISA	Blood	(Lieberman, [66]
	70	*H. influenzae, S. pneumoniae, P. aeruginosa, S. aureus*	Culture	Serum, BALF	[39]
Italy	193	*S. pneumoniae, S. pyogenes, S. aureus, M. catarrhalis, H. influenzae*	Culture	Sputum	[18]
	256	*Chlamydophila pneumoniae*	MIF	Throat swab	[13]
	65	*H. parainfluenzae, H. influenzae, M. catarrhalis, S. pneumoniae, Enterobacteriaceae, Pseudomonas spp., S. aureus*	Culture	Sputum	[12]
	64	*H. influenzae, S. pneumoniae, M. catarrhalis, S. aureus, P. aeruginosa, Enterobacter spp.*	Culture, ELISA	Sputum, Blood	[89]
	217	*S. pneumoniae*	PCR	Sputum	[68]
Japan	46	*S. pneumoniae, H. influenzae, M. pneumoniae, Chlamydophila pneumoniae, S. aureus*	Culture, Real-time PCR	NS, Sputum	[116]
The Netherlands	171	*H. influenzae, S. pneumoniae, P. aeruginosa*	Culture	Sputum	[45]
	116	*S. pneumoniae, H. influenzae, M. catarrhalis, P. aeruginosa, S. aureus*	Culture	Sputum	[128]
	248	*Legionella nonpneumophila*	Real-time PCR	Sputum	[31]
	37	*H. influenzae, M. catarrhalis, S. pneumoniae*	Culture	Sputum	[10]
	18	*Nontypeable H. influenza*	Culture	Sputum	[44]
	1288	*S. pneumoniae, H. influenza, P. aeruginosa*	Culture	Sputum, BALF, TBA	[16]
New Zealand	33	*Streptococcus pseudopneumoniae*	Culture	Sputum	[55]
Pakistan	105	*H. influenzae, S. pneumoniae*	Culture	Sputum	[40]
Poland	35	*Peptostreptococcus, Fusobacterium, Bacteroides, Prevotella, Propionibacterium, Actinomyces, Eubacterium, Porphyromonas, Peptococcus*	Culture	Sputum	[53]
	28	*H. parainfluenzae, H. influenzae*	Culture	Sputum	[56]
	109	*A. baumannii, S. aureus*	Culture	Sputum	[83]

Table 1 (continued)

Location	No. of samples	Bacterial species	Method	Type of sample	References
	53	*Enterobacter sakazakii, Enterobacter aerogenes, Enterobacter cloacae, M. lacunata, S. epidermidis, S. cohnii, S. aureus, Klebsiella pneumoniae, Stenotrophomonas maltophilia, Pseudomonas putida, P. aeruginosa, Acinetobacter lwoffii, E. coli*	Culture	Oral swab	[97]
Saudi Arabia	139	*M. catarrhalis, H. influenzae, P. aeruginosa*	Culture, CXR	Sputum	[3]
South Korea	201	*H. pylori*	ELISA	Blood	[62]
	217	*H. influenzae, S. pneumoniae, P. aeruginosa, M. catarrhalis, Klebsiella pneumoniae, E. coli, S. aureus, Stenotrophomonas maltophilia*	Culture, PCR	Sputum	[98]
Spain	116	*S. pneumoniae, S. aureus, H. influenzae, Neisseria spp., Corynebacterium spp., Candida spp.*	Culture	PSB, BAL	[17]
	50	*S. pneumoniae, H. influenzae, M. catarrhalis, C. pneumoniae, Proteus mirabilis, Serratia marcescens, Enterobacter spp., Pseudomonas spp.*	Culture	TBA, PSB, BALF	[120]
	91	*H. influenzae, P. aeruginosa, S. pneumoniae, M. catarrhalis*	Culture	Sputum	[73]
	90	*H. influenzae, S. pneumoniae, M. catarrhalis, P. aeruginosa*	Culture	Sputum	[76]
	267	*H. influenzae, S. pneumoniae, M. catarrhalis, Enterobacteria, P. aeruginosa, S. aureus*	Culture	Sputum	[103]
	40	*H. influenzae, S. pneumoniae, M. catarrhalis, E. coli, Enterobacter spp., P. aeruginosa*	Culture	Sputum, PSB	[119]
	13	*P. aeruginosa*	Culture	Sputum, Blood	[69]
	50	*P. aeruginosa*	Culture	Sputum	[77]
	318	*S. pneumoniae, L. pneumoniae, H. influenzae, P. aeruginosa, M. catarrhalis, Enterobacteria, S. aureus,*	Culture, MIF	Blood, Sputum	[59]
	398	*S. pneumoniae*	Culture	Blood, BALF, TBA, Sputum	[79]
	85	*M. pneumoniae, H. influenzae, C. pneumoniae, S. pneumoniae, P. aeruginosa, M. catarrhalis, Klebsiella pneumoniae, E. coli, Enterobacter intermedius*	Culture, PCR, ELISA	Sputum, NS, Blood	[105]
	111	*P. aeruginosa, H. influenzae, S. pneumoniae, M. catarrhalis, S. aureus*	Culture, Real-time PCR	Sputum	[32]
	116	*S. pneumonia*	Culture, PCR	Sputum	[33]
	118	*P. aeruginosa*	Culture	Sputum	[41]
	124	*P. aeruginosa, H. Influenzae, M. catarrhalis, S. pneumoniae, E. coli, Achromobacter xylosoxidans, S. aureus*	Culture	Sputum, Blood	[15]
	536	*P. aeruginosa, S. pneumoniae*	Culture	Sputum, Blood	[14]
	111	*P. aeruginosa*	Culture	Sputum	[43]
Sweden	43	*H. influenza*	Culture	Sputum	[125]
Tunisia	100	*Chlamydophila pneumoniae*	ELISA, MIF	Blood, Sputum	[70]

Table 1 (continued)

Location	No. of samples	Bacterial species	Method	Type of sample	References
Turkey	106	*H. influenzae, Streptococcus pneumoniae, M. catarrhalis*	Culture	Sputum	[127]
	49	*Chlamydophila pneumoniae*	Culture, MIF	Sputum	[74]
	38	*α-haemolytic streptococci, Niesseria spp, Candida spp., S. pneumoniae, S. aureus, P. aeruginosa, H. influenza*	Culture, MIF	Blood, NS, Sputum	[54]
	39	*S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus, Neisseria spp., Haemophilus spp.*	Culture	BALF	[126]
	114	*S. pneumoniae, H. influenzae, M. catarrhalis, Klebsiella pneumoniae, P. aeruginosa, E. coli, S. aureus, A. baumannii, M. catarrhalis, M. pneumonia*	Culture, PCR	Sputum	[5]
United Kingdom	29	*S. pneumoniae, H. parainfluenzae, M. catarrhalis, P. aeruginosa*	Culture	Sputum	[93]
	145	*H. influenzae, M. catarrhalis, S. pneumoniae, S. aureus, P. aeruginosa*	Culture, PCR	Sputum	[7]
	373	*Chlamydophila pneumoniae, Legionella pneumophila, M. pneumoniae, H. influenzae, S. pneumoniae, M. catarrhalis*	Culture, Real-time PCR	Sputum	[42]
	126	*Mycobacterium spp.*	Culture	Lung tissue, Sputum	[23]
	174	*H. influenzae, M. catarrhalis, S. pneumoniae, S. aureus*	Culture, Real-time PCR	Sputum	[6]
USA	81	*S. pneumoniae, H. influenzae, P. aeruginosa, M. catarrhalis,*	Culture	Sputum	[109]
	104	*M. catarrhalis*	Culture, ELISA	Sputum, Serum	[1]
	15	*H. influenzae*	Culture	Sputum	[25]
	150	*Nontypeable H. influenzae, S. pneumoniae, M. catarrhalis, P. aeruginosa*	Culture, ELISA	Sputum, Blood	[113]
	126	*P. aeruginosa*	Culture, PCR, ELISA	Sputum, Blood	[78]
	39	*M. catarrhalis*	Culture, ELISA	Sputum	[91]
	8	*P. aeruginosa, Klebsiella pneumoniae, S. aureus, Enterobacter aerogenes, S. maltophilia, H. influenzae, S. pneumoniae, M. pneumoniae, Chlamydophila pneumoniae, Campylobacter mucosalis, Helicobacter cetorum, Lactobacillus kitasatonis, Bacillus clausii, S. constellatus, Streptococcus milleri, Lactobacillus perolens, Lactobacillus sakei, Leptospira interrogans, Brevundimonas diminuta, Arcobacter cryaerophilus*	Culture, Real-Time PCR, Microarray	BALF	[49]
	153	*M. catarrhalis*	Culture	Sputum	[90]
	64	*H. influenzae, M. catarrhalis, S. pneumoniae, P. aeruginosa*	Culture, PCR	Sputum	[30]
	12	*P. aeruginosa, H. influenzae, M. catarrhalis, Klebsiella spp., P. fluorescens, S. pneumoniae,*	Culture, Real-time PCR	Sputum	[50]
	1352	*S. pneumoniae, H. influenzae, P. aeruginosa, M. catarrhalis, Klebsiella pneumoniae*	Culture	Sputum	[108]

NS nasopharyngeal swab, *TBA* tracheobronchial aspirate, *TA* tracheal aspirate, *BA* bronchial aspirate, *PSB* protected specimen brush

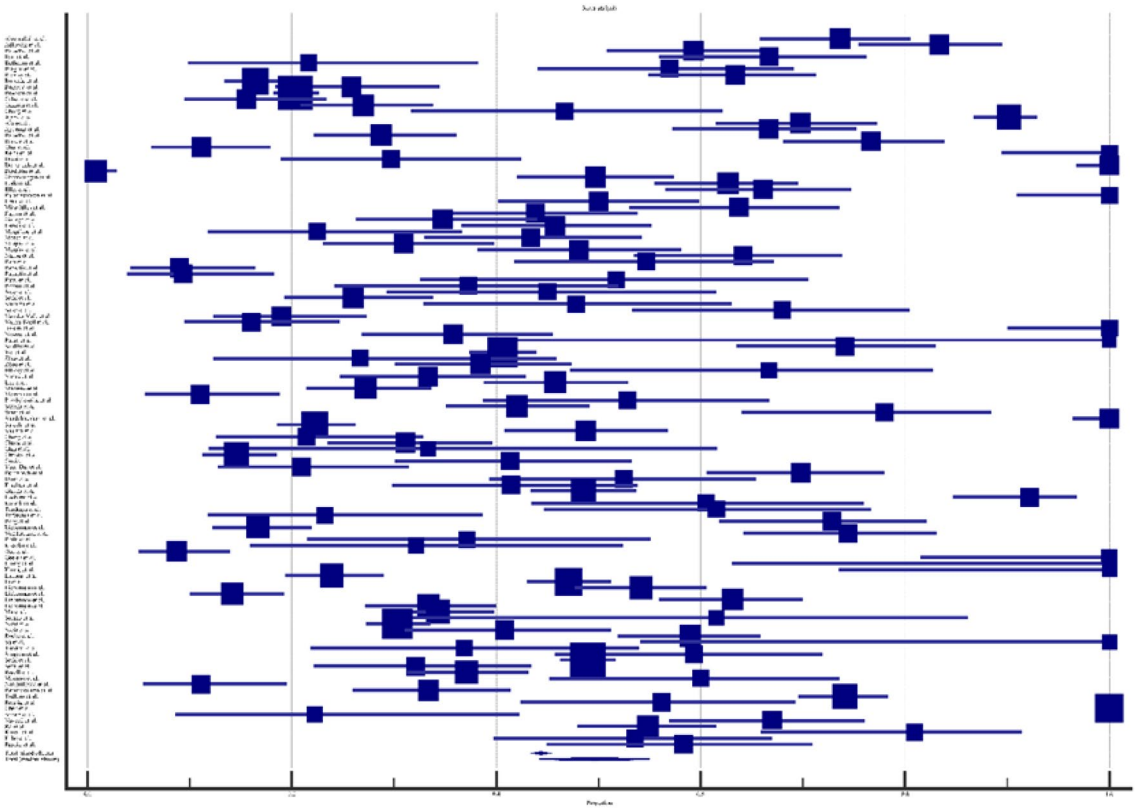

Fig. 2 Forest plot indicates the estimation for the prevalence of bacterial infection in COPD patients

indirectly detected the pathogens using nonspecific polyclonal antibodies [110]. As an important note regarding the serology assay studies, although serology could indicate passive infections and not necessarily active infection, these studies using serology assays (mostly for detecting *M. pneumoniae*, *M. catarrhalis*, and *Chlamydophila pneumonia*) evaluated current active bacterial infections in AECOPD patients. Regarding the advantages and disadvantages of both culture and molecular methods, it seems that the combination of these two methods may give more reliable results [61]. Of note, three studies used microarray as the high-throughput technique for bacterial detection. Due to the high capacity of the microarray to specifically identify a wide range of microbial species as well as their different characteristics, using microarray developed for simultaneous detection of many bacterial species and strains would be of great attention in the future. A mechanism related to bacterial infection is the bacterial load. In COPD exacerbations, the bacterial load increases with a significant decrease in microbiome complexity [11, 37]. In one study, Sethi et al. demonstrated that the bacterial load of *H. haemolyticus, M. catarrhalis,* and *H. influenzae* in the sputum of AECOPD patients was significantly different from stable patients. In addition, they indicated a significant negative correlation between the sputum bacterial load for *H. parainfluenzae* and *S. pneumoniae* and the exacerbation occurrence, whereas *H. influenzae* was detected in high concentrations in AECOPD patients [112]. In terms of clinical specimens, sputum was the most prevalent sample in this meta-analysis. Although sputum is not an ideal representative for lower respiratory tract microflora (due to the possible contamination by oral flora), the sampling simplicity and feasibility have introduced sputum as the most prevalent lower respiratory sample. In addition, bronchoalveolar lavage and protected specimen brush sampling may be applicable only for the milder severity states of AECOPD but not for a more severe disease state. Although the application of PCR or real-time PCR methods in sputa could correctly detect oral flora, it would be unable to ascertain if these are commensals or have converted into a pathogenic state. One of the main factors in COPD pathogenesis is airway inflammation

Table 2 Subgroup analyses for assessing the pooled prevalence of bacterial infections in COPD patients

Characteristics	Categories	No. of studies	Pooled prevalence (95% CI)	Heterogeneity test (Q, I^2%, P)	Publication bias (Begg's Test, P; Egger's test, P)	Model
All studies	–	118	0.4959 (0.4418, 0.55)	(6615, 98.23%; $P<0.0001$)	(Begg's Test, 0.37; Egger's test, 0.01)	Random
Year of Publication	≤2005	32	0.50 (0.4156, 0.5845)	(756, 8.95.9%; $P<0.0001$)	(Begg's Test, 0.19; Egger's test, 0.10)	Random
	>2005	86	0.4939 (0.4281, 0.5598)	(5858, 98.55%; $P<0.001$)	(Begg's Test, 0.11; Egger's test, 0.001)	Random
Age average	≤60 years	11	0.4526 (0.2546, 0.6587)	(1012, 99.01%; $P<0.001$)	(Begg's Test, 0.41; Egger's test, 0.001)	Random
	>60 years	72	0.5114 (0.446, 0.5767)	(3695, 98.08%; $P<0.001$)	(Begg's Test, 0.03; Egger's test, 0.02)	Random
Biological sample	Sputum	97	0.4943 (0.4328, 0.5558)	(6003, 98.4%; $P<0.001$)	(Begg's Test, 0.03; Egger's test, 0.01)	Random
	Blood	33	0.4594 (0.3581, 0.5623)	(1684, 98.1%; $P<0.001$)	(Begg's Test, 0.29; Egger's test, 0.08)	Random
	BALF	11	0.5090 (0.3172, 0.6994)	(491, 97.971%; $P<0.001$)	(Begg's Test, 0.40; Egger's test, 0.17)	Random
	Others	12	0.4047 (0.2877, 0.5274)	(234, 95.31%; $P<0.001$)	(Begg's Test, 0.66; Egger's test, 0.29)	Random
Detection method	PCR and real-time PCR	24	0.4632 (0.350, 0.5784)	(280, 94.99%; $P<0.001$)	(Begg's Test, 0.10; Egger's test, 0.05)	Random
	ELISA	21	0.5099 (0.3767, 0.6423)	(800, 97.5%; $P<0.001$)	(Begg's Test, 0.15; Egger's test, 0.09)	Random
	Culture	99	0.4956 (0.4375, 0.5538)	(5596, 98.25%; $P<0.001$)	(Begg's Test, 0.05; Egger's test, 0.05)	Random
	MIF	7	0.3542 (0.2021, 0.5232)	(139, 95.68%; $P<0.001$)	(Begg's Test, 0.09; Egger's test, 0.04)	Random
Risk factor	unknown	99	0.4667 (0.4176, 0.5161)	(3746, 97.38%; $P<0.001$)	(Begg's Test, 0.09; Egger's test, 0.05)	Random
	Inflammation	10	0.6535 (0.4729, 0.8158)	(205, 95.63%; $P<0.001$)	(Begg's Test, 0.23; Egger's test, 0.11)	Random
	Diabetes mellitus	9	0.6135 (0.2848, 0.8925)	(2296, 99.65%; $P<0.001$)	(Begg's Test, 0.31; Egger's test, 0.14)	Random
	Others	10	0.4034 (0.2944, 0.5175)	(285, 96.85%; $P<0.001$)	(Begg's Test, 0.89; Egger's test, 0.25)	Random

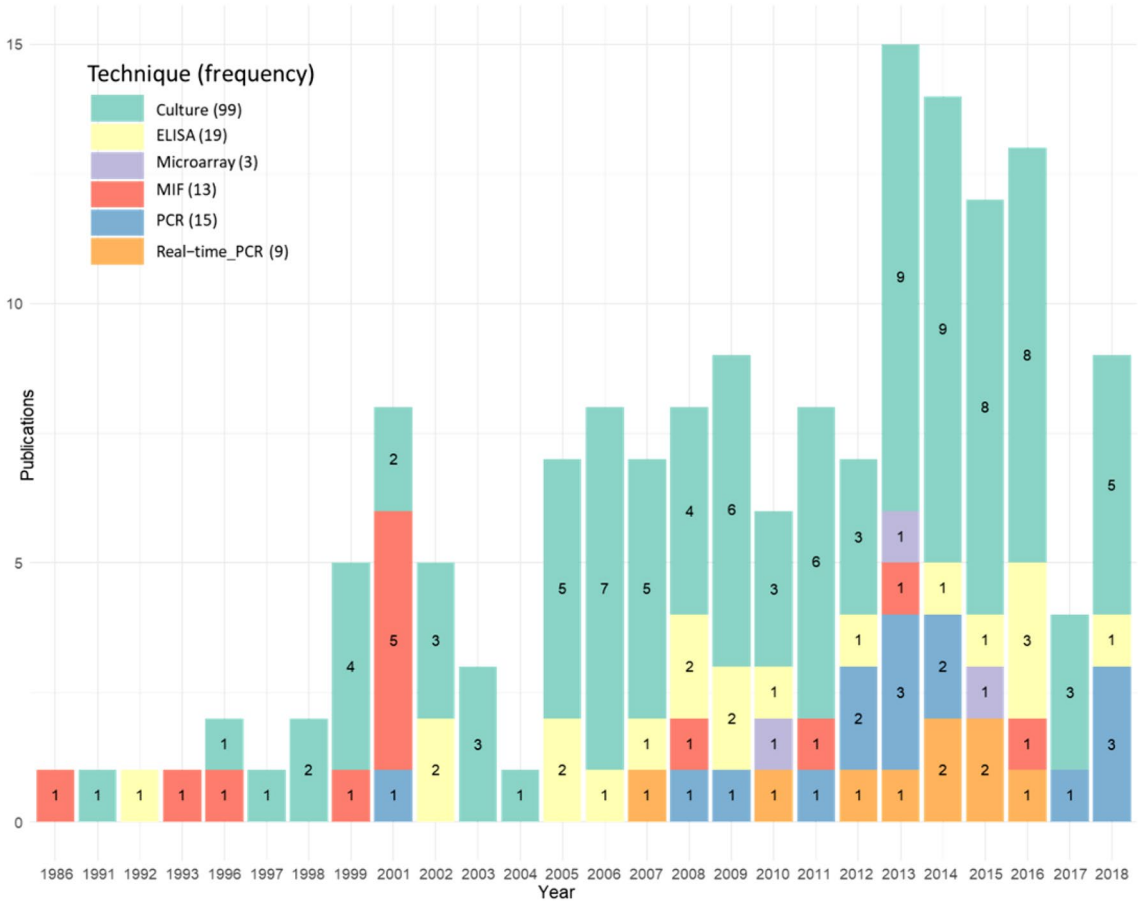

Fig. 3 Time trend of applying detection methods for bacterial infections in AECOPD

leading to progressive airway injuries, though producing inflammatory mediators such as cytokines by T cells, macrophages, and neutrophils [11, 57]. Studies indicated that bacterial infection can trigger airway immune system that resulted in inflammation [45]. A study showed that the neutrophilic inflammation (including neutrophil elastase, TNF-α, and IL-8) in COPD-mediated bacterial exacerbation was higher than nonbacterial exacerbation [111]. Neutrophil migration into airways may occur due to bacterial products. The elastase produced by neutrophils can act synergistically with bacterial products to inhibit tracheobronchial ciliary function [11, 110]. After inflammation, another risk factor considered here was diabetes. This disease in individuals with COPD more occurs than in healthy persons. The association between COPD and diabetes is varied and different studies known that diabetes affects 2–37% of COPD patients [102].

Conclusion

The current study provides the first overall bacterial infection prevalence in AECOPD patients worldwide and information about bacterial species in different geographical areas. It seems that besides other risk factors such as viral infections and environmental conditions, bacterial infections caused mainly by the dysbiotic respiratory microbiome may consider as the major risk factor of AECOPD for which more accurate and applicable detection and therapeutic methods. Further studies with more developed methods must be performed for understanding the exact role of bacterial agents in AECOPD.

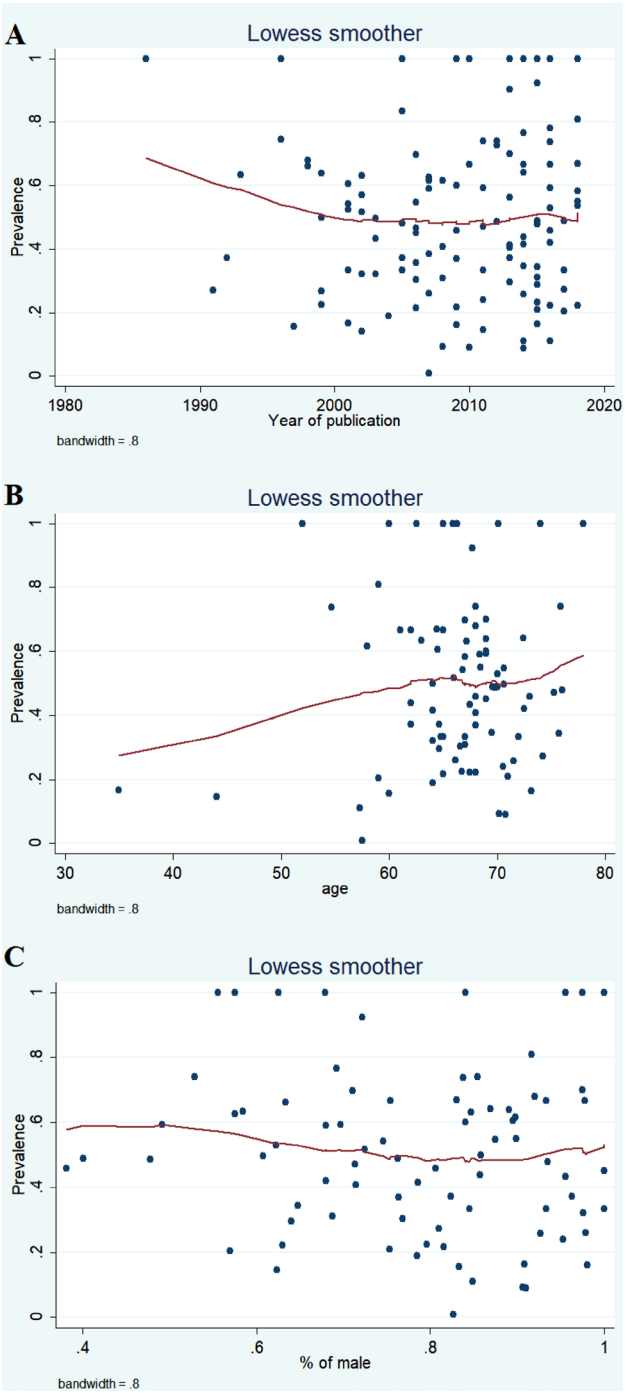

Fig. 4 Prevalence of bacterial infection in COPD patients over time (**a**), with age (**b**), and gender (**c**)

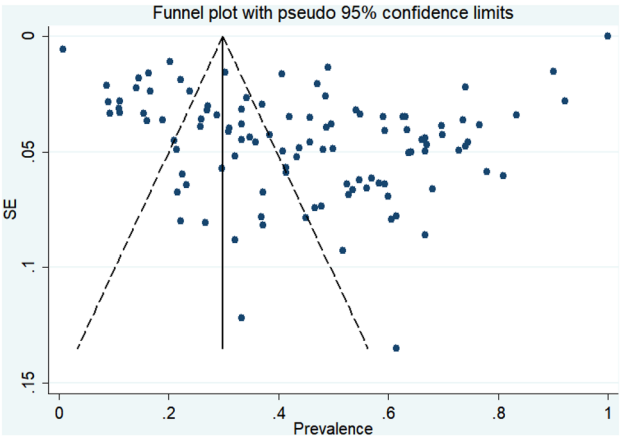

Fig. 5 Funnel plot of each study's standard error (*y*-axis) against each study's frequency of bacterial infection in COPD patients. The line indicates the overall mean frequency of bacterial infection

Author contributions Study design: SAJ and AA. Acquisition of data: MM, MM, and JS. Analysis and interpretation of data: MM. Drafting of the manuscript: MM and AA. Critical revision of the manuscript for important intellectual content: SAJ, JS, and MM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest with the contents of this article.

Ethical approval This study does not need ethical approval and patient consent. All analyses were according to previously published studies.

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