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Article *in* New Microbes and New Infections · July 2021

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ORIGINAL ARTICLE

Bacterial coinfection among coronavirus disease 2019 patient groups: an updated systematic review and meta-analysis

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Abstract

The pandemic of severe acute respiratory syndrome coronavirus 2 raised the attention towards bacterial coinfection and its role in coronavirus disease 2019 (COVID-19) disease. This study aims to systematically review and identify the pooled prevalence of bacterial coinfection in the related articles. A comprehensive search was conducted in international databases, including MEDLINE, Scopus, Web of Science, and Embase, to identify the articles on the prevalence of bacterial coinfections in COIVD-19 patients from 1 December 2019 until 30 December 2020. All observational epidemiological studies that evaluated the prevalence of bacterial coinfections in patients with COVID-19 were included without any restriction. Forty-two studies including a total sample size of 54,695 were included in the analysis. The pooled estimate for the prevalence of bacterial coinfections was 20.97% (95% CI: 15.95–26.46), and the pooled prevalence of bacterial coinfections was 5.20% (95% CI: 2.39–8.91) for respiratory subtype and 4.79% (95% CI: 0.11–14.61) for the gastrointestinal subtype. The pooled prevalence for Eastern Mediterranean Regional Office and South-East Asia Regional Office was 100% (95% CI: 82.35–100.00) and 2.61% (95% CI: 1.74–3.62). This rate of coinfection poses a great danger towards patients, especially those in critical condition. Although there are multiple complications and adverse effects related to extensive use of antibiotics to treat patients with COVID-19, it seems there is no other option except applying them, and it needs to be done carefully.
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Keywords: Coinfection, coronavirus, COVID-19, meta-analysis, systematics review
Original Submission: 10 May 2021; **Revised Submission:** 1 June 2021; **Accepted:** 23 June 2021
Article published online: 1 July 2021

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Introduction

Bacterial coinfection played an important role in escalating the morbidity and mortality rate during previous viral outbreaks and pandemics [1]. Most patient's death during 1918–1919 influenza pandemic was related to bacterial co-pathogens rather than the virus itself [2]. During H1N1 pandemics, several studies recorded the high prevalence of secondary and bacterial

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https://doi.org/10.1016/j.nmni.2021.100910

coinfection [3]. It was also reported that people with bacterial coinfection showed high number of mortalities. Critically ill patients showed greater percentage of coinfection compared with hospitalized patients [4]. Previous experience during other respiratory viral infections supported the use of antibiotics; so, at the onset of COVID-19 infection, early guidelines for COVID-19 treatment suggested the use of antibiotics in all the patients [5,6]. Identification of prevalence of bacterial coinfection is crucial for the initial empiric antibiotic treatment, in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients. The different possible complications could occur because of the extensive implication of antibiotics in patients. Antibacterial resistance is one of the challenges because of this amount of antibiotics use, which can affect the societies in the next years [7,8]. But because of similar clinical and radiological manifestation of some respiratory bacterial pathogen, such as *pneumococcal, staphylococcal*, *and Klebsiella* with COVID-19, it is difficult to decide which patients should receive antibiotics treatment, especially at the first encounter with the patients [9].

Materials and methods

All steps in this systematic review and meta-analysis study were based on preferred reporting items for systematic review and meta-analysis guidelines [10] and registered in the International Prospective Register of Systemic Reviews with CRD42021240030. Using related keywords such as "COVID-19", "Coronavirus", "SARS-CoV-2 infection", "SARS-CoV-2", "Polymicrobial Infection", "Bacterial AND Coinfections", "Bacterial AND Secondary Infections", and "Mixed Infections", all related articles were retrieved.

Method of literature search

A complete and comprehensive search without any language restrictions was conducted in international databases, including MEDLINE, Scopus, Web of Science, and Embase, to identify the articles on the prevalence of bacterial coinfections in patients with COIVD-19 from 1 December 2019 until 30 December 2020, in English and non-English language. Other sites, including Medrxiv and Social Science Research Network (SSRN), were also searched to identify the unofficially published researches. The text words and Medical Subject Headings (MeSH) terms of COIVD-19 and coinfections were used to search. The PICOTS in our study was as follows:

Population: Patients with COVID-19
Intervention: None
Comparison: None
Outcome: Prevalence of bacterial coinfections
Time: from 1 December 2019 until 30 December 2020
Study design: Observational study

The search strategy is described below that is applied based on PICOTS for MEDLINE (MeSH) and then used in other databases:

1. COVID-19 [text word] OR COVID-19 [Mesh term]
2. Coronavirus Disease-19 [text word] OR Coronavirus Disease-19 [Mesh term]
3. SARS-CoV-2 infection [text word] OR SARS-CoV-2 infection [Mesh term]
4. 1 OR 2 OR 3
5. Prevalence [text word] OR Prevalence [Mesh term]
6. Frequency [text word] OR Frequency [Mesh term]
7. Incidence [text word] OR Incidence [Mesh term]
8. 5 OR 6 OR 7
9. Coinfection [text word] OR Coinfection [Mesh term]
10. Mixed Infection [text word] OR Mixed Infection [Mesh term]
11. Polymicrobial Infection [text word] OR Polymicrobial Infection [Mesh term]
12. Bacterial Coinfection [text word] OR Bacterial Coinfection [Mesh term]
13. 9 OR 10 OR 11 OR 12
14. 4 AND 8 AND 13

Google Scholar was used to accessing grey literature. Also, a bacteriology expert was consulted to find relevant articles, and also, we try to find other articles by handsearching from the references list of relevant articles. Then, all data were imported to Endnote X6, and after removing the duplicated articles, the remaining studies has been screening in three steps. In the first step, the titles were reviewed, and if the article was relevant, then the abstract and then the full text of the articles were reviewed. The three steps were followed independently by two raters, "Reza Pakzad" and "Saber Soltani", and interrater discrepancies were resolved based on the third person's opinion, "Iraj Pakzad". Blinding and task separation were applied in study procedure selection. The interrater agreement was 89%.

Inclusion and exclusion criteria

All observational epidemiological studies, including cohort, cross-sectional, and case series studies around the world, that examined the prevalence of bacterial coinfections in patients with COVID-19 were included without any restriction. Case reports and case series with less than ten sample sizes were excluded. Also, editorials, commentaries, case–control, randomized clinical trial, and reviews were excluded.

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Data extraction

In addition to general information, including the name of authors, year, country, study design, sample size or number of patients with COVID-19, age, sex, and other data including number and type of bacterial coinfections were extracted in all studies. Herein, patients with COVID-19 (confirmed cases based on molecular tests such as PCR) with even a single bacterial coinfection were considered in the study.

Variable definition

Bacteria types were classified based on transmission way and clinical signs. Countries were categorized based on the latest WHO definition that includes the following six regions: Regional Office for Africa, Regional Office of Americas (AMRO), Regional Office for the Eastern Mediterranean, Regional Office for Europe, Regional Office for South-East Asia (SEARO), and the Regional Office for the Western Pacific (WPRO).

Quality assessment

The Newcastle-Ottawa Scale for case reports/case series and observational study was used to assess the quality of the included studies [11]. This scale has three sections: 1, selection (4 items, maximum score: 4 points); 2, confounder (1 item, maximum score: 1 point); and 3, exposure (2 items, maximum score: 2 points). The studies were evaluated by two raters (Reza Pakzad and Saber Soltani) independently, and a total score was calculated for each study. The studies were then assigned to one of the following categories accordingly: very good studies: 6–7 scores; good studies: 4–5 scores; satisfactory studies: 2–3 scores; unsatisfactory studies: 0–1 score [12].

Statistical analysis

All analysis was conducted with Stata software 14.0 (College Station, TX). As previous studies [13–16], the number of COVID-19 cases, the prevalence of bacterial coinfections in COVID-19, and its different bacterial types were extracted. Heterogeneity was determined using Cochran's Q test of heterogeneity, and the I^2 index was used to quantify heterogeneity. Following the Higgins classification approach, I^2 values above 0.7 were considered as high heterogeneity. The pooled prevalence with 95% CI was calculated using the "metaprop" command, and to estimate the pooled prevalence, we used the random effects model. It should be noted the "Freeman-Tukey double-arcsine transformation" method is used for estimating 95% CI to keep the value between 0% and 100%. The meta-regression analysis was used to examine age, WHO region, and sample size as factors affecting heterogeneity among studies. The "metabias" command was used to check the publication bias. If there was any publication bias, the prevalence rate was adjusted with the "meta-trim" command using the trim-and-fill method. In all analyses, a significance level of 0.05 was considered.

Results

Overall, 8700 studies were found through databases, and 138 studies were identified through other sources (SSRN: 4, Medrxiv: 8, grey literature: 8, bacteriology expert: 3, and handsearching: 115). After excluding redundant articles, 7260 studies remained. Screening was done in three steps. In the first step, 5136 studies were excluded after reviewing the titles, and 2124 articles remained. After reading abstracts, 1732 studies were excluded from the list. Then, the full text of the remaining 392 studies was reviewed, and 350 studies were excluded. Finally, 42 studies [17–58] with a total sample size of 54,695 were included in the analysis. The flowchart of this selection process is shown in Fig. 1, and the characteristic of the studies was showed in Table 1 and Supplement 1. European region had the highest number of studies (15 studies), and Eastern Mediterranean Region and Western Pacific had the lowest number of studies. All studies were published during the year 2020. The minimum and maximum age range of the subjects was for a study by Wu *et al.* (mean age = 6 years) and a study by D'Onofrio *et al.* (mean age = 73 years), respectively. The study setting assessment indicates 25 (59.53%) of the studies are cohort (prospective and retrospective), 12 (28.57%) are case series (prospective and retrospective), and 5 (11.9%) are cross-sectional.

Pooled prevalence of bacterial coinfections in patients with COVID-19

The prevalence of bacterial coinfections in all included studies was listed in Table 1. Also, Fig. 2 showed the forest plot for the prevalence of bacterial coinfections. The minimum and maximum reported prevalence of bacterial coinfections were reported by Hazra *et al.* (prevalence: 0%; 95% CI: 0–0.80) in Chicago [27] and by Sharifipour *et al.* (prevalence: 100%; 95% CI: 82.35–100) in Iran [47]. Based on Fig. 2 using random effects model approach, the pooled estimate for the prevalence of bacterial coinfections was 20.97% (95% CI: 15.95–26.46). This means that in overall, of every 100 people with COVID-19, 16–26 people have bacterial coinfections.

Pooled prevalence of bacterial coinfections based on different subgroups

Fig. 3 shows the pool prevalence of bacterial coinfections based on bacteria subtype, different place, and study type. The pooled prevalence of bacterial coinfections was (5.20%; 95% CI:

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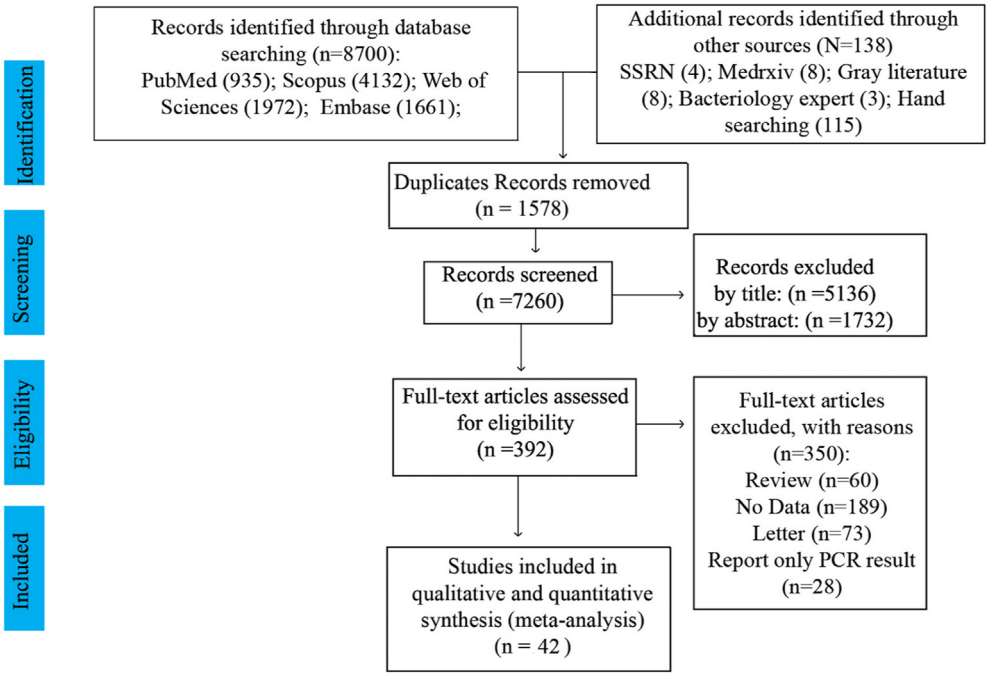

FIG. 1. PRISMA flow diagram of the process of study selection for analysis.

2.39–8.91) for respiratory subtype and (4.79%; 95% CI: 0.11–14.61) for gastrointestinal subtype. The most and least pooled prevalence of bacterial coinfections based on study design was estimated in case series studies with 42.82% (95% CI: 18.42–69.19) and in cross-sectional studies with 1.82% (95% CI: 0.0–8.88), respectively. The pooled prevalence for WPRO and AMRO was 20.15% (95% CI: 8.54–34.96) and 13.97% (95% CI: 2.58–32.09), respectively. More detail was shown in Fig. 3.

Heterogeneity and meta-regression

Table 2 presents the results of the heterogeneity. According to Cochran's Q test of heterogeneity, there was significant heterogeneity among studies ($p < 0.001$). The I^2 index for total bacterial coinfections was 99%. According to meta-regression results, the age (coefficient: −0.205; $p = 0.643$), sample size (coefficient: −0.001; $p = 0.215$), and WHO region size (coefficient: −5.304; $p = 0.262$) had no significant effect on heterogeneity among studies (Fig. 4A and B). Type of the study (coefficient: 20.274; $p = 0.007$) had significant effect on heterogeneity among studies.

Publication bias

Based on the results of Begg's test, a significant publication bias was observed for total bacterial coinfections (Z score: 4.11; $p < 0.001$). Therefore, the trim-and-fill–adjusted pooled prevalence of bacterial coinfections (23.55%; 95% CI: 18.38–28.73) was generated, which was not significantly different from the original pooled prevalence (20.97%; 95% CI: 15.95–26.46), and the mean results have robustness.

Discussion

Critically ill patients are more prone to bacterial coinfection compared with other infected individuals. Critically ill patients demonstrated 8.1% of coinfection, which is slightly more compared with 5.9% in hospitalized individuals [59]. Another meta-analysis article showed that 7% of patients were infected with bacterial pathogens [60]. Bacterial coinfection in the meta-analysis study was observed in 3.5% of patients. Bacterial secondary infection was identified in 14.3% of patients. This meta-analysis indicated that the most common bacterial coinfection amongst patients with COVID-19 were *Mycoplasma pneumonia, Pseudomonas aeruginosa*, and *Haemophilus influenzae*. This study also mentioned 3% of the patients were coinfected with viruses. The median age ranges from 42 to 63 years in most of the studies included in this meta-analysis [60].

The overall prevalence of bacterial coinfection in patients with COVID-19 was 6.9%. Nearly all the studies indicated that the patients received some kind of antibiotics [59]. Bacterial coinfection plays an undeniable role in increasing morbidity and mortality rate in viral pandemics, such as influenza [61].

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TABLE 1. Characteristics of the included studies in present systematic review and meta-analysis

Author	Country	Study Design	Publication year	Mean or Age	Sample Size	Bacterial Coinfections Prevalence, % (95% CI)
Zhu *et al.* [58]	China	Retrospective case series	2020	51	257	91.83 (87.78–94.87)
Blasco *et al.* [17]	Spain	Retrospective case series	2020	64	183	0.55 (0.10–3.10)
Contou *et al.* [20]	France	Retrospective case series	2020	61	92	95.65 (89.24–98.80)
Sarinoglu *et al.* [45]	Turkey	Cross-sectional	2020	NA	30	6.67 (0.82–22.7)
Chauhdary *et al.* [18]	Brunei	Case series	2020	NA	141	3.55 (1.16–8.8)
Cheng *et al.* [19]	China	Retrospective cohort	2020	36	62	40.32 (28.50–53.55)
D'Onofrio *et al.* [21]	Belgium	Cohort	2020	73	110	2.73 (0.57–7.76)
Fu *et al.* [22]	China	Retrospective cohort	2020	NA	101	4.95 (1.63–11.18)
Garcia-Vidal *et al.* [23]	Spain	Retrospective cohort	2020	62	989	2.93 (1.97–4.18)
Dir *et al.* [24]	USA	Retrospective cohort	2020	57	350	1.71 (0.63–3.69)
Gupta *et al.* [26]	India	Retrospective cohort	2020	36	1073	2.50 (1.29–3.90)
Hazra *et al.* [27]	USA	Cross-sectional	2020	NA	459	0.0 (0.0–0.80)
Hirotsu *et al.* [28]	Japan	Cross-sectional	2020	NA	40	0.0 (0.0–8.81)
Hughes *et al.* [29]	UK	Retrospective case series	2020	69.5	836	3.23 (2.14–4.66)
Intra *et al.* [30]	Italy	Retrospective cohort	2020	NA	61	68.85 (55.71–80.10)
Karami *et al.* [31]	The Netherlands	Retrospective cohort	2020	70	925	0.86 (0.37–1.70)
Kim *et al.* [32]	USA	Cross-sectional	2020	46.9	116	0.0 (0.0–3.13)
Kimmig *et al.* [33]	USA	Retrospective cohort	2020	46.9	111	37.84 (28.80–47.54)
Li *et al.* [34]	China	Retrospective cohort	2020	66.2	1495	20.60 (18.58–22.74)
Li *et al.* [35]	China	Case series	2020	57	32	31.25 (16.12–50.1)
Liu *et al.* [36]	China	Retrospective case series	2020	46.5	20	20.0 (5.73–43.66)
Lv *et al.* [37]	China	Retrospective cohort	2020	62	354	14.12 (10.67–18.19)
Ma *et al.* [38]	China	Case series	2020	45.5	250	9.60 (6.25–13.95)
Massey *et al.* [39]	USA	Retrospective case series	2020	62.3	790	55.44 (51.90–58.95)
Motta *et al.* [40]	Multiplace[a]	Cohort	2020	NA	69	7.25 (2.39–16.11)
Neto *et al.* [25]	USA	Retrospective cohort	2020	66	242	19.10 (14.27–24.53)
Verroken *et al.* [52]	The Netherlands	Cohort	2020	NA	32	18.75 (7.21–36.44)
Nori *et al.* [41]	USA	Retrospective cohort	2020	62	152	44.80 (36.40–52.35)
Pandey *et al.* [51]	India	Cross-sectional	2020	NA	120	13.33 (7.82–20.75)
Porretta *et al.* [42]	Italy	Cohort	2020	67.4	331	9.67 (6.71–13.37)
Ripa *et al.* [43]	Italy	Cohort	2020	64	731	7.25 (5.48–9.38)
Rothe *et al.* [44]	Germany	Retrospective cohort	2020	63.5	140	76.43 (68.52–83.19)
Sepulveda *et al.* [46]	USA	Retrospective cohort	2020	NA	28,011	3.80 (3.58–4.30)
Sharifipour *et al.* [47]	Iran	Case series	2020	67.1	19	100.0 (82.35–100.0)
Sharov *et al.* [48]	Russia	Retrospective case series	2020	NA	147	75.51 (67.74–82.22)
Sy *et al.* [49]	Philippine	Cohort	2020	44.21	12,513	0.90 (0.74–1.80)
Tadolini M *et al.* [50]	Multiplace	Cohort	2020	48	49	85.71 (72.76–94.6)
Wu *et al.* [53]	China	Retrospective case series	2020	6	74	47.30 (35.57–59.25)
Youngs *et al.* [54]	UK	Cohort	2020	59	36	30.56 (16.35–48.11)
Yu *et al.* [55]	Sweden	Cohort	2020	NA	2240	10.90 (8.87–11.41)
Zha *et al.* [56]	China	Retrospective cohort	2020	57	874	2.52 (1.58–3.79)
Zhang *et al.* [57]	China	Retrospective cohort	2020	64.76	38	57.89 (40.82–73.69)

Abbreviation: NA, not available.
[a]Belgium, Brazil, France, Italy, Russia, Singapore, Spain, and Switzerland.

Bacterial coinfection among patients infected with influenza virus has been reported up to 30% [1].

One of the important aspects of determining the incidence and prevalence of bacterial coinfection is related to antibiotic prescription for patients with COVID-19 [25]. Although the use of antibiotics in coronavirus patients is rapidly growing, the effectiveness of them is under questioning. A number of studies have questioned the amount of prescribing antibiotics for the patients and have opinioned that this will cause us another great challenge, which is antibiotic resistance, but on the other hand, utilization of antibiotic in the pandemic situation is inevitable for different reasons, such as the difficulties of excluding bacterial coinfection and the possibility of secondary infection in patients [62].

More than 70% of patients with COVID-19 received some kind of antibiotics with a focus on broad-spectrum agents, such as fluoroquinolones and third-generation cephalosporins [59]. Bacterial coinfection was also reported in previous pandemics. During the 2009 influenza (H1N1) pandemic, patients in intensive care units showed up to 30% of bacterial coinfection. The most commonly identified pathogens were *S. aureus and S. pneumoniae* [1,63].

In contrast, in the recent COVID-19 pandemic, it becomes more and more clear that gram-negative and atypical bacteria are the most isolated bacteria from SARS-CoV-2 patients. A meta-analysis study showed that the most common organisms reported by the studies were *Mycoplasma* species, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* [59].

Gram-negative microorganisms were also reported as the most frequent cause of lower respiratory tract infection. *Pseudomonas aeruginosa* was the most common isolated bacteria among patients with ventilator-associated pneumonia (38%) and tracheobronchitis (33%) [64]. Another systematic review and meta-analysis showed that the commonest bacteria were Mycoplasma pneumonia, Pseudomonas aeruginosa, and Haemophilus influenzae [60].

But there are controversial data about SARS-CoV-2 coinfection with these bacteria. Langford *et al.* showed that these

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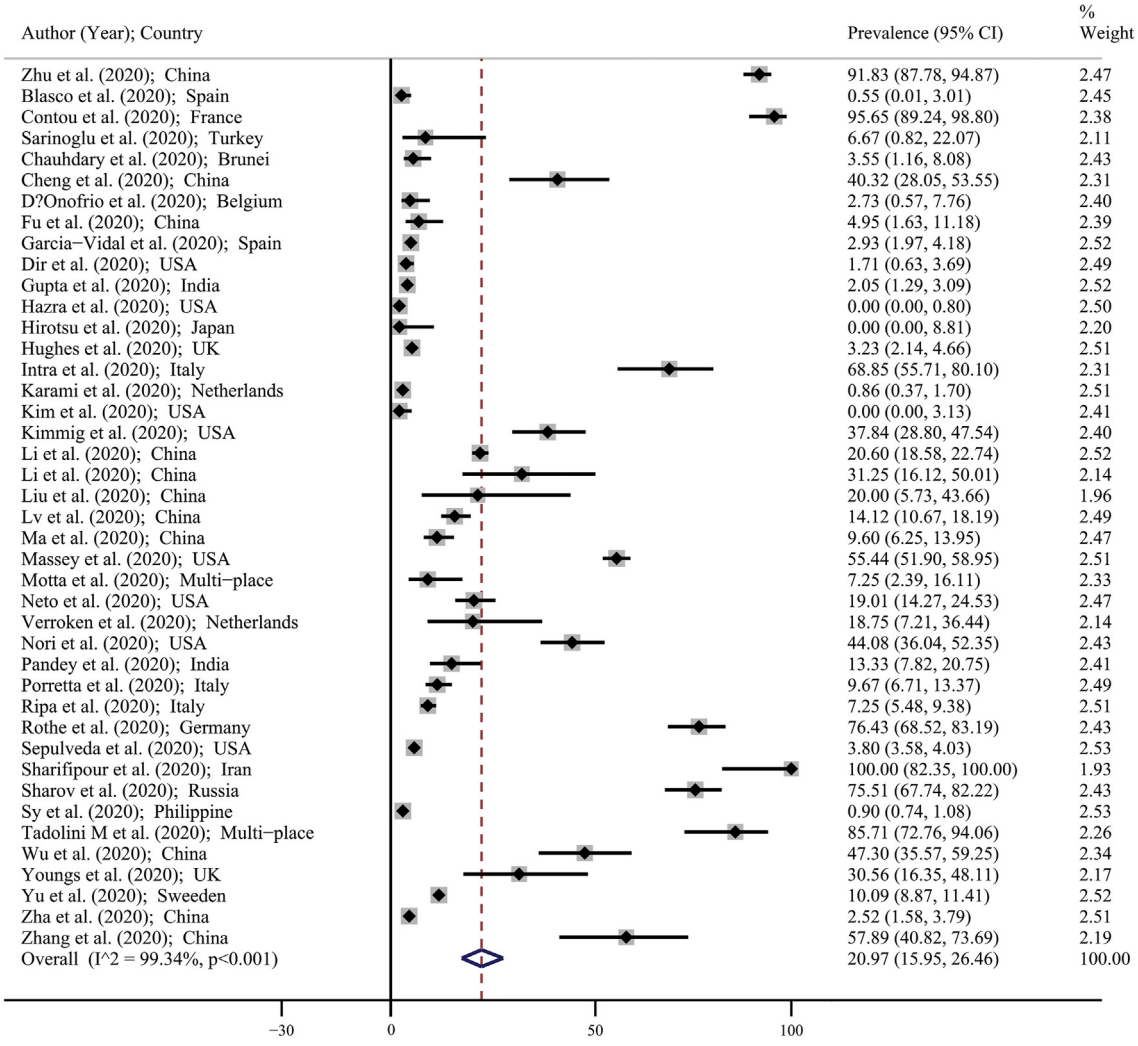

FIG. 2. Forest plot for the prevalence of bacterial coinfections in patients with COVID-19 based on a random effects model. Each study identifies by the first author (year) and country. Each line segment's midpoint shows the prevalence estimate, length of line segment indicates 95% CI in each study, and diamond mark illustrates the pooled estimate.

bacterial pathogens are not common amongst people with COVID-19, yet another meta-analysis study reported the rate of *S. aureus*/COVID-19 coinfection was 25.6%, and the proportion of COVID-19/MRSA *S. aureus* was 53.9%, which has been collected from five different studies [59,65].

Johns' Hopkins scientists in a multicentre study found only 1.2% of the patients had bacterial coinfection, which is less frequent than in other studies. The researchers suggested that their varied data may be related to inclusion and exclusion criteria used by them [66]. They also mentioned their sampling time could be an effective factor compared with other studies. Their study was conducted in spring, whereas other studies were implemented during winter in Europe and China. They also indicated variation in vaccination background of sample population against pneumococcal infection, and this may also affect the coinfection prevalence [67].

Although it is not the main focus of our study, it is worth mentioning the coinfection of other microorganisms, such as viruses and fungi with SARS-CoV-2. The rate of fungal coinfection with SARS-CoV-2 has been reported diversely.

A systematic review and meta-analysis conducted by Jackson S. Musuuza found the prevalence of fungal coinfections, 4% and fungal superinfections, 8% among patients with COVID-19 [68]. In contrast, another study reported that the overall pooled proportion of patients with coinfection was only 0.12 [69]. It should be mentioned that *Aspergillus and* Candida species were the most frequently reported among patients with COVID-19. Viral coinfections and viral superinfections were reported 10%

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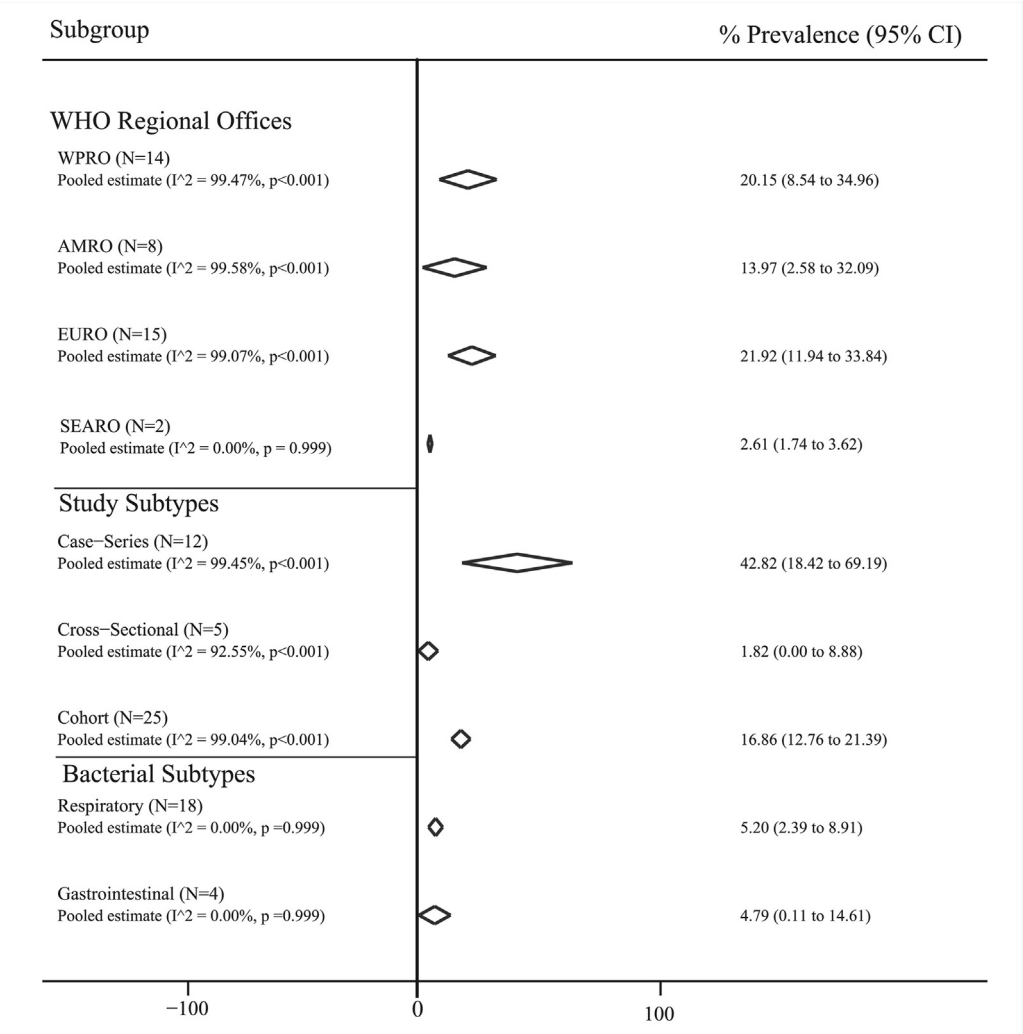

FIG. 3. Pooled prevalence with 95% CI and heterogeneity indices of bacterial coinfections in patients with COVID-19 based on the type of the bacteria, different regional places (AMRO: Regional Office of Americas; EURO: Regional Office for Europe; SEARO: Regional Office for South-East Asia; EMRO: Regional Office for the Eastern Mediterranean; WPRO; Regional Office for the Western Pacific) and the type of the study. The diamond mark illustrates the pooled prevalence, and the length of the diamond indicates the 95% CI. *N* is the number of the study in the analysis. The prevalence for EMRO (*N* = 1) was 100 % (95% CI: 82.35–100.00).

and 4%, respectively, and the most frequently identified viruses among patients were influenza type A (22.3%), influenza type B (3.8%), and respiratory syncytial virus (3.8%) [68].

TABLE 2. The univariate meta-regression analysis on the hertogenisity of the determinants in included studies for bacterial coinfections in patients with COVID-19.

Variables	Coefficient	95% CI	p value
Age (year)	−0.205	−1.103 to 0.692	0.643
WHO region (score)	−5.304	−14.739 to 4.131	0.262
Sample size (number)	−0.001	−0.003 to 0.001	0.215
Type of the study (score)	20.274	5.768 to 34.781	0.007

Coding of WHO region: 1 = EMRO; 2 = EURO; 3 = AMRO; 4 = WPRO; 5 = SEARO; Coding of type of the study: 1 = cross-sectional; 2 = cohort; 3 = case series.

Our results showed the 5.2% pooled prevalence for respiratory bacterial coinfection and gastrointestinal subtype had 4.79% amongst patients with COVID-19, which are in consistent with previous research reported the ranged of bacterial coinfection between 3.1% and 7%. We also found that case series studies reported the highest level of coinfection compared with cross-sectional studies, which showed the lowest rate. From geographical viewpoint, we acquired some interesting results. Our analysis exhibit that the WPRO has 20.15% and AMRO had 13.97% of coinfection, which shows a great difference between these regions. Our meta-analysis showed the pooled estimate for the prevalence of bacterial coinfections was 20.97%. Our results clearly indicate the high

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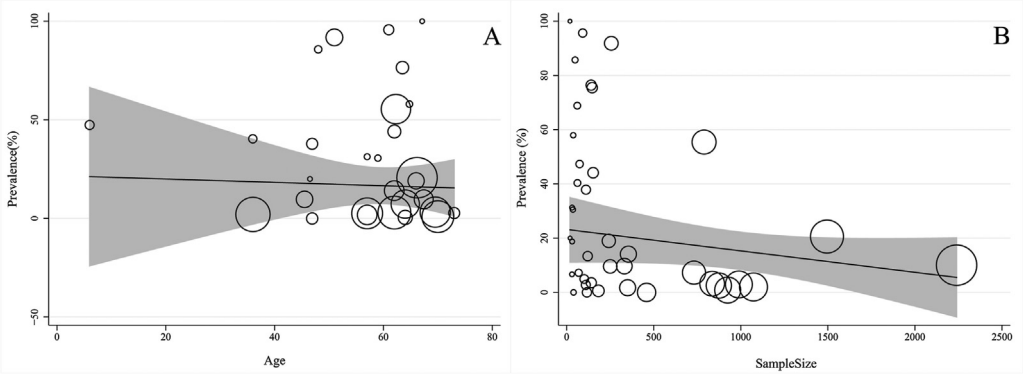

FIG. 4. Association among prevalence of age (A) and sample size (B) with the prevalence of bacterial coinfections by means of meta-regression. The size of circles indicates the precision of each study. There is no significant association with respect to the prevalence of bacterial coinfections with age and sample size.

prevalence of bacterial pathogens amongst patients with COVID-19. Therefore, we came to the conclusion that prescribing antibiotics for patients with COVID-19 based on the high percentage of bacterial coinfection is inevitable.

The currents evidence is against the massive use of antibiotics to treat patients with COVID-19 in both hospitalized and critically ill state, but it has been mentioned in this manuscript that the circumstances can be different from one to another patient situation, and it also should be noted that the data are still progressing almost every day, so it would be wise for clinicians to use antibiotics with cautions and always update themselves with the latest research.

Escalation in patient's body temperature, longer fever duration, anhelation, gastrointestinal-related symptoms, intensive care unit attending, ventilation treatment, glucocorticoid therapy, severity in disease situation, and prolongation in hospitalization time were reported as different sequences of clinical outcome linked to bacterial coinfection [67]. The data have reported the elderly patients with high level of inflammatory factors and worse lymphopenia and cardiovascular comorbidities have a higher chance of being infected with bacterial infection. In addition, these patients had worsened illness situations and showed multiple set of system failure [29,67].

The laboratory results of patients with COVID-19 have several clinical risk factors related to coinfection. A case–control study reported that C-reactive protein and median neutrophil to lymphocyte ratio were significantly higher in case compared to controls. However, there was not any statistical significance in procalcitonin levels in patients with COVID-19 with bacterial infection compared with people without bacterial infection [69]. Shengyang *et al.* found that patients with COVID-19 with bacterial coinfection had substantially increase in their procalcitonin. This article also confirms the increase in C-reactive protein in the patients [67].

Similar to other studies, our research had some limitations. (1) we would like to perform the gender-specific estimation, but it was not possible because of insufficient data in the primary studies; (2) we estimated the pooled prevalence based on WHO regional office and tendency to examine the spatial analysis in different geographical regions based on available methods [70–72], but because of the infrequent studies number, this estimation will not be robust. Also, in the SEARO subgroup, we have only two studies, and this may cause unrobust estimates. Doing a comprehensive search and estimate the pooled prevalence based on different bacteria subtypes was the present study's strengths.

Conclusion

Because of the proven track of bacterial coinfection in increasing morbidity and mortality rate in previous viral outbreaks and pandemics, proving information about the incidence and prevalence rate of them are crucial for health administrators and clinicians, but the contrary data prove that various factors affect the final output of the studies, and setting clinical guidelines or prescribing medication based on the results of different research should be done carefully and considering all the factor, which yield effect on the final results. Considering the multiple complications and adverse effects of extensive use of antibiotics in patients with COVID-19, it seems there is no other option except applying them, but it needs to be done carefully.

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Authors' contributions

S.S. contributed to study design, creation of models, and management activities to annotate (produce metadata), specifically writing the initial draft (including substantive translation).

S.F. contributed to data collection and writing the article, developed the theory, and performed the computations, specifically writing the initial draft (including substantive translation).

M.Z. contributed to data collection, writing the article, and conducting a research and investigation process.

R.S. contributed to data collection, writing the article, and conducting a research and investigation process.

A.J. contributed to data collection, writing the article, and conducting a research and investigation process.

S.A.R. contributed to data collection and writing the article.

I.P. contributed to study design and writing the article.

F.A. contributed to data collection and writing the article.

P.M. contributed to management and coordination responsibility for the research activity planning and execution, study design, data analysis, development or design of methodology, and creation of models.

R.P. contributed to design and perform the idea, data analysis, development or design of methodology, and creation of models.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at doi:10.1016/j.nmni.2021.100910.

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