PLOS ONE

Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis

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Abstract

Introduction

The recovery of other pathogens in patients with SARS-CoV-2 infection has been reported, either at the time of a SARS-CoV-2 infection diagnosis (co-infection) or subsequently (superinfection). However, data on the prevalence, microbiology, and outcomes of co-infection and superinfection are limited. The purpose of this study was to examine the occurrence of co-infections and superinfections and their outcomes among patients with SARS-CoV-2 infection.

Patients and methods

We searched literature databases for studies published from October 1, 2019, through February 8, 2021. We included studies that reported clinical features and outcomes of co-infection or superinfection of SARS-CoV-2 and other pathogens in hospitalized and non-hospitalized patients. We followed PRISMA guidelines, and we registered the protocol with PROSPERO as: CRD42020189763.

Results

Of 6639 articles screened, 118 were included in the random effects meta-analysis. The pooled prevalence of co-infection was 19% (95% confidence interval [CI]: 14%-25%, I^2 = 98%) and that of superinfection was 24% (95% CI: 19%-30%). Pooled prevalence of pathogen type stratified by co- or superinfection were: viral co-infections, 10% (95% CI: 6%-14%); viral superinfections, 4% (95% CI: 0%-10%); bacterial co-infections, 8% (95% CI: 5%-11%); bacterial superinfections, 20% (95% CI: 13%-28%); fungal co-infections, 4% (95% CI: 2%-7%); and fungal superinfections, 8% (95% CI: 4%-13%). Patients with a co-infection or superinfection had higher odds of dying than those who only had SARS-CoV-2 infection (odds ratio = 3.31, 95% CI: 1.82–5.99). Compared to those with co-infections, patients with

superinfections had a higher prevalence of mechanical ventilation (45% [95% CI: 33%-58%] vs. 10% [95% CI: 5%-16%]), but patients with co-infections had a greater average length of hospital stay than those with superinfections (mean = 29.0 days, standard deviation [SD] = 6.7 vs. mean = 16 days, SD = 6.2, respectively).

Conclusions

Our study showed that as many as 19% of patients with COVID-19 have co-infections and 24% have superinfections. The presence of either co-infection or superinfection was associated with poor outcomes, including increased mortality. Our findings support the need for diagnostic testing to identify and treat co-occurring respiratory infections among patients with SARS-CoV-2 infection.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is associated with high morbidity and mortality [1, 2]. Current evidence shows that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is primarily transmitted through respiratory droplets [3, 4] from symptomatic, asymptomatic, or pre-symptomatic individuals [4, 5]. Similar to other respiratory pathogens, such as influenza, where approximately 25% of older patients get secondary bacterial infections [6, 7], both superinfections and co-infections with SARS-CoV-2 have been reported [8–10]. However, there is scarce data on the frequency of co-infection and superinfections by viral, bacterial, or fungal infections and associated clinical outcomes among patients infected with SARS-CoV-2 [8–10].

We define co-infection as the recovery of other respiratory pathogens in patients with SARS-CoV-2 infection at the time of a SARS-CoV-2 infection diagnosis and superinfection as the subsequent recovery of other respiratory pathogens during care for SARS-CoV-2 infection. Two previous reviews have examined the prevalence of bacterial and fungal co-infection or superinfection in SARS-CoV-2 infected patients [11, 12]. In addition, prior work suggests outcome differences in patients with co-infections vs. superinfections. For example, Garcia-Vidal et al., showed that SARS-CoV-2 infected patients with superinfection s had a longer length of hospital stay (LOS) and higher mortality, while those with co-infections had a higher frequency of admission to the ICU [13].

Diagnostic testing and therapeutic decision-making may be affected by the presence of co-infection or superinfection with SARS-CoV-2 and other respiratory pathogens.

Therefore, we conducted a systematic review and meta-analysis to examine the occurrence and outcomes (e.g., LOS) of respiratory co-infections and superinfections among patients infected with SARS-CoV-2.

Materials and methods

We conducted this systematic review in accordance with the Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. We registered this review with PROSPERO: CRD42020189763 [15]. The protocol is available as a S1 File.

Data sources and searches

With the help of a health sciences librarian (LC), we searched PubMed, Scopus, Wiley, Cochrane Central Register of Controlled Trials, Web of Science Core Collection, and CINAHL

Plus databases to identify English-language studies published from October 1, 2019, through February 8, 2021. We executed the search in PubMed and translated the keywords and controlled vocabulary for the other databases, and additional articles were added from reference lists of pertinent articles. The following keywords were used for the search: "coronavirus","coronavirus infections", "HCoV", "nCoV", "Covid", "SARS", "COVID-19", "2019 nCoV", "nCoV 19", "SARS-CoV-2", "SARS coronavirus2", "2019 novel corona virus", "Human", "pneumonia", "influenza", "severe acute respiratory syndrome", "co-infection", "Superinfection", "bacteria", "fungus", "concomitant", "pneumovirinae", "pneumovirus infections", "respiratory syncytial viruses", "metapneumovirus", "influenza", "human", "respiratory virus", "bacterial Infections", "viral infection", "fungal infection", "upper respiratory", "oxygen inhalation therapy", "intensive care units", "nursing homes", "subacute care", "skilled nursing", "intermediate care", "patient discharge", "mortality", "morbidity" and English filter. A complete description of our search strategy is available as a S2 File.

Study selection

Citations were uploaded into Covidence®, an online systematic review software for the study selection process. Two authors (JSM and LW) independently screened titles and abstracts and read the full texts to assess if they met the inclusion criteria. The authors met and discussed any articles where there was conflict and decided to either include or exclude such articles. Inclusion criteria were randomized clinical trials (RCTs), quasi-experimental and observational human studies that reported clinical features and outcomes of co-infection or superinfection of SARS-CoV-2 (laboratory-confirmed) and other pathogens–fungal, bacterial, or other viruses–in hospitalized and non-hospitalized patients. We excluded studies that did not report co-infection or superinfection, editorials, reviews, qualitative studies, those published in a non-English language, articles where full texts were not available, and non-peer-reviewed preprints.

Data extraction

Three reviewers (JSM, LW, and VP) independently abstracted data from individual studies using a standardized template. We abstracted data on study design/methodology, location and setting (intensive care unit [ICU], inpatient non-ICU, or outpatient, where applicable), study population, use of antibiotics, proportion of patients with co-infections, implicated pathogens, method of detection of co-infections and superinfections (laboratory-verified or clinical features only), type of infection (bacterial, viral, or fungal), and outcomes of co-infected patients (death, mechanical ventilation, discharge disposition, length of hospital stay, or mild illness). Discrepancies were resolved by discussion between the three abstractors.

Risk of bias assessment

Risk of bias assessment was conducted by three authors (JSM, LW, and VP) independently. We used two study quality assessment tools, one specific to case series [16], and one for non-case series study designs [17].

The tool for case series examines four domains: selection, ascertainment, causality, and reporting [16]. The selection domain helps to assess whether participants included in a study are representative of the entire population from which they arise. Ascertainment assesses whether the exposure and outcome were adequately ascertained. Causality assesses the potential for alternative explanations and specifically for our study whether the follow-up was long enough for outcomes to occur. Reporting evaluates if a study described participants in sufficient detail to allow for replication of the findings. This tool consists of eight items, but only

five were applicable to our study [16]. When an item was present in a study, a score of 1 was assigned and 0 if the item was missing. We added the scores (minimum of 0 and a maximum of 5) and assigned the risk of bias as follows: low risk (5), medium risk (3–4), high risk (0–2).

For non-case series studies, we used the Modified Downs and Black risk assessment scale to assess the quality of cohort studies and RCTs [17]. This scale consists of 27 items that assess study characteristics, such as internal validity (bias and confounding), statistical power, and external validity. We scored studies as low risk (score 20–27, medium risk (score 15–19), or high risk (score ≤14).

Data synthesis and analysis

The primary outcome was the prevalence of co-infections or superinfections by viral, bacterial, or fungal respiratory infections and SARS-CoV-2. We examined whether co-infection or superinfection was associated with an increased risk for the following patient outcomes: 1) mechanical ventilation, 2) admission to the ICU, 3) mortality and LOS.

We estimated the proportion of patients with co-infection or superinfection of viral, bacterial, and fungal respiratory infections and SARS-CoV-2. We anticipated a high level of heterogeneity given the novelty of COVID-19 and potential differences in testing and management of COVID-19 in the healthcare systems of the countries where the studies were conducted. We conducted all statistical analyses using Stata software, version 16.0 (Stata Corp. College Station, Texas). We used the "metan" and "metaprop" commands in Stata to estimate the pooled proportion of co-infection and superinfection and COVID-19 using a random effects model (Der-Simonian Laird) [18, 19]. We stabilized the variance using the Freeman-Tukey arcsine transformation methodology in order to correctly estimate extreme proportions (i.e., those close to 0% or 100%) [18]. We assessed heterogeneity using the I^2 statistic. Frequencies of outcome variables and study characteristics were estimated using descriptive statistics. For example, in studies where data on co-infecting or super-infecting pathogens were reported, we extracted and tallied the number of different pathogens reported. We calculated the proportion of pathogens using the number of pathogens as the numerator and the total number of pathogens of each type (bacteria, viruses, and fungi) from all the studies as the denominator.

We did not assess for publication bias because standard methods, such as funnel plots and associated tests, were developed for comparative studies and therefore do not produce reliable results for meta-analysis of proportions [20, 21].

Results

Our search yielded 14457 records; we excluded 7818 duplicates and screened 6639 articles. At the abstract and title review stage, we excluded 6273 articles, leaving 366 articles for full-text review. Of these, 118 articles met the inclusion criteria and were included in this meta-analysis. The most frequent reason for exclusion of studies at the full-text review stage was the absence of superinfection or co-infection data (Fig 1).

Approximately half of the studies (60/118) were retrospective cohort studies, 35% (42/118) were cases series, and 9% (11/118) were prospective cohort studies. There were two case-control studies, two cross-sectional studies, and one clinical trial. The majority of the studies were conducted in China (42% [49/118)]) and the US (15% [18/118]). Most of the studies were conducted in a mixed setting (i.e., ICU and non-ICU setting; 72% [85/118]) and 92% (108/118) were conducted exclusively in hospitalized patients. The majority of studies were conducted among adults (73% [86/118]). Sixty-seven (57%) of the included studies reported that patients included had co-infections, 37% (44/118) reported superinfections, and 6% (7/118) reported both co-infections and superinfections among patients. Viral co-infections in patients were
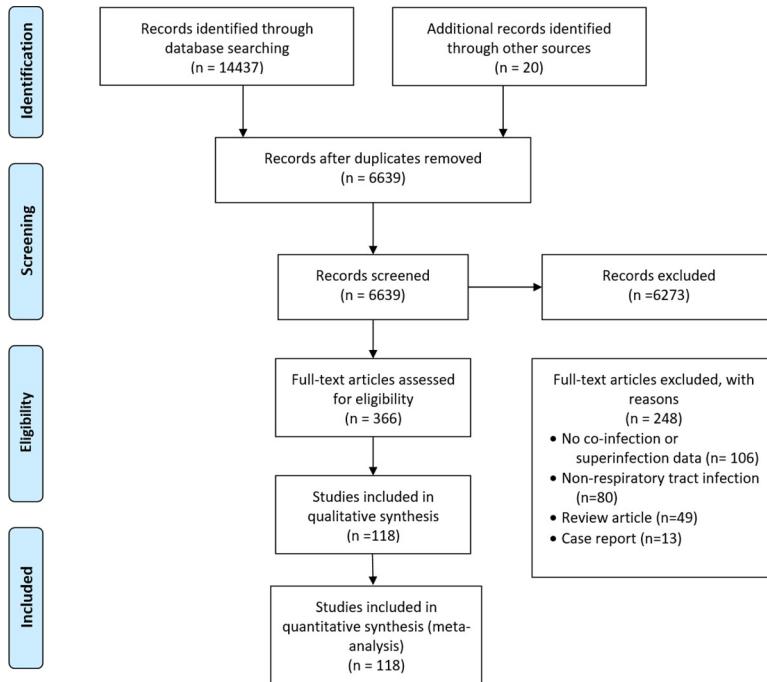
Fig 1. Study selection flow diagram: Adapted from the PRISMA guideline [11].

reported in 67% (55/81) of the studies, bacterial infections in 74% (78/105), fungal in 48% (35/73) of studies. Not all of the 118 studies reported data on viral, bacterial or fungal infections (Table 1). Seventy percent (83/118) of the studies reported data on antibiotic use. Of these, antibiotics were administered in 98% (81/83) of the studies.

The pooled prevalence of co-infection was 19% (95% confidence interval [CI]: 14%-25%; $I^2 = 98$%). The highest prevalence of co-infection was observed among non-ICU patients at 29% (95% CI: 14%-46%), while it was 18% (95% CI: 12%-25%) among combined ICU and non-ICU patients, and 16% (95% CI: 8%-25%) among only ICU co-infected patients (Fig 2). The pooled prevalence of superinfection was 24% (95% CI: 19%-30%), with the highest prevalence among ICU patients (41% [95% CI: 24%-58%]) (Fig 3).

Pooled prevalence of pathogen type stratified by co- or superinfection was: viral co-infections, 10% (95% CI: 6%-14%) and viral superinfections, 4% (95% CI: 0%-10%); bacterial co-infections, 8% (95% CI: 5%-11%) and bacterial superinfections, 20% (95% CI: 13%-28%); and fungal co-infections, 4% (95% CI: 2%-7%) and fungal superinfections, 8% (95% CI: 4%-13%) (S1–S3 Figs).

Seventy-eight studies reported data on specific organisms associated with co-infection or superinfection in COVID-19 patients (Table 2). Among patients with co-infections, the three most frequently identified bacteria were *Klebsiella pneumoniae* (9.9%), *Streptococcus pneumoniae* (8.2%), and *Staphylococcus aureus* (7.7%). The three most frequently identified viruses among co-infected patients were influenza type A (22.3%), influenza type B (3.8%), and respiratory syncytial virus (3.8%). For fungi, *Aspergillus* was the most frequently reported among those co-infected.

Among those with superinfections, the three most frequently identified bacteria were *Acinetobacter spp.* (22.0%), *Pseudomonas* (10.8%), and *Escherichia coli* (6.9%). For viruses, Rhinovirus was the most frequently identified among those with superinfections, and for fungi, *Candida sp.* was the most frequent (18.8%).

Table 1. Main characteristics of included studies.

Study	Study design	Country	Setting	Number of patients	Age group of patients	Gender (% male)	ICU (%)	Patients who were ventilated n (%)	Patients who died n (%)	Viral co-infections n (%)	Bacterial co-infection n (%)	Fungal co-infections n (%)	Risk of bias
Arentz, 2020 [22]	Case series	USA	ICU[a]	21	Adults	52	100	15 (71)	11 (52)	3 (14)	1 (50)	0 (0)	Medium
Barrasa, 2020 [23]	Case series	Spain	ICU	48	Adults	56	100	45 (94)	16 (33)	0 (0)	6 (13)	0 (0)	Low
Campochiaro, 2020 [24]	Prospective cohort	Italy	ICU and non-ICU	65	Adults	29	6	25 (38)	16 (25)	0 (0)	1 (2)	0 (0)	Low
Chen, 2020 [25]	Case series	China	ICU	99	Adults	68	100	17 (17)	11 (11)	0 (0)	1 (1)	4 (4)	Medium
Cuadrado-Payán, 2020 [26]	Case series	Spain	ICU	4	Adults	75	75	3 (75)	0 (0)	4 (100)	0 (0)	0 (0)	High
Ding, 2020 [27]	Case series	China	Non-ICU	115	Adults	NR[b]	0	0 (0)	0 (0)	5 (4)	0 (0)	0 (0)	Medium
Dong, 2020 [28]	Case series	China	Non-ICU	11	Adults/children	54	0	1 (9)	0 (0)	1 (9)	0 (0)	0 (0)	Medium
Du, 2020 [29]	Case series	China	ICU	109	Adults	67.9	48.6	33 (30)	109 (100)	0 (0)	NR	NR	Low
Fan, 2020 [30]	Retrospective cohort	China	ICU and non-ICU	50	Adults	83	54	23 (46)	12 (24)	0 (0)	5 (10)	5 (10)	Low
Feng, 2020 [31]	Case series	China	ICU and non-ICU	476	Adults	56.9	26	70 (15)	38 (8)	0 (0)	35 (7)	0 (0)	Medium
Garazzino, 2020 [32]	Retrospective cohort	Italy	ICU and non-ICU	168	Children	55.9	1.1	2 (1)	0 (0)	10 (6)	1 (0.5)	0 (0)	Low
Gayam, 2020 [33]	Case series	USA	ICU and non-ICU	350	Adults	33	NR	NR	NR	0 (0)	1 (0.3)	0 (0)	Medium
Huang, 2020 [34]	Case series	China	ICU and non-ICU	41	Adults	73	32	4 (10)	6 (15)	0 (0)	1 (2)	0 (0)	Medium
Kakuya, 2020 [35]	Case series	Japan	Non-ICU	3	Children	100	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	Low
Khodamoradi, 2020 [36]	Case series	Iran	Non-ICU	4	Adults	75	0	0 (0)	0 (0)	4 (100)	0 (0)	0 (0)	Medium
Kim, 2020 [37]	Retrospective cohort	USA	Non-ICU	115	Adults/children	45	0	0 (0)	0 (0)	25 (22)	0 (0)	0 (0)	Low
Koehler, 2020 [38]	Case series	Germany	ICU	19	Adults	NR	100	NR	3 (16)	2 (11)	0 (0)	5 (26)	Medium
Lian, 2020 [39]	Retrospective cohort	China	ICU and non-ICU	788	Children/Adults	52	3	18 (2)	0 (0)	NR	0 (0)	0 (0)	Low
Lin, 2020 [8]	Case series	China	ICU and non-ICU	92	Adults	NR	NR	NR	NR	6 (7)	NR	NR	Medium
Liu, 2020 [40]	Retrospective cohort	China	ICU and non-ICU	12	Children/Adults	66	NR	6 (50)	NR	0 (0)	2 (17)	0 (0)	Low
Lv, 2020 [41]	Retrospective cohort	China	ICU and non-ICU	354	Adults	49	NR	NR	11 (3)	1 (0.3)	32 (9)	6 (2)	Low
Ma, 2020 [42]	Retrospective cohort	China	NR	93	Adults	55	NR	NR	44 (47)	46 (49)	0 (0)	0 (0)	Low
Mannheim, 2020 [43]	Case series	USA	ICU and non-ICU	64	Children	56	11	NR	NR	3 (5)	1 (2)	0 (0)	Medium
Mo, 2020 [44]	Case series	China	ICU and non-ICU	155	Adults	55	NR	36 (23)	22 (14)	13 (8)	2 (1)	0 (0)	Medium
Nowak, 2020 [9]	Case series	USA	ICU and non-ICU	1204	Adults	56	NR	NR	NR	36 (3)	0 (0)	0 (0)	Medium
Ozaras, 2020 [45]	Case series	Turkey	ICU and non-ICU	1103	Adults	50	NR	NR	NR	6 (0.5)	0 (0)	0 (0)	Medium
Palmieri, 2020 [46]	Retrospective cohort	Italy	ICU and non-ICU	3032	Children/Adults	67	NR	NR	3032 (100)	NR	NR	NR	Low

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Table 1. (Continued)

Study	Study design	Country	Setting	Number of patients	Age group of patients	Gender (% male)	ICU (%)	Patients who were ventilated n (%)	Patients who died n (%)	Viral co-infections n (%)	Bacterial co-infection n (%)	Fungal co-infections n (%)	Risk of bias
Peng, 2020 [47]	Retrospective cohort	China	ICU and non-ICU	75	Children	58	NR	NR	0 (0)	8 (11)	31 (41)	0 (0)	Low
Pongpirul, 2020 [48]	Case series	Thailand	ICU and non-ICU	11	Adults	54	NR	0 (0)	0 (0)	2 (18)	5 (45)	0 (0)	Low
Richardson, 2020 [49]	Case series	USA	ICU and non-ICU	5700	Adults	60	14.2	1151 (20)	553 (10)	39 (0.7)	3 (0.1)	0 (0)	Low
Sun, 2020 [50]	Retrospective cohort	China	ICU and non-ICU	36	Children	61	NR	NR	1 (3)	1 (3)	1 (3)	0 (0)	Medium
Tagarro, 2020 [51]	Retrospective cohort	Spain	ICU and non-ICU	41	Children	44	9.7	4 (10)	0 (0)	2 (5)	0 (0)	0 (0)	Low
Wan, 2020 [52]	Case series	China	ICU and non-ICU	135	Adults	53	NR	28 (21)	1 (0.7)	NR	NR	NR	Medium
Wang Y, 2020 [53]	Case series	China	ICU and non-ICU	55	Adults	40	0	0 (0)	0 (0)	1 (2)	1 (2)	1 (3)	Low
Wang L, 2020 [54]	Case series	China	ICU and non-ICU	339	Adults	49	NR	NR	65 (19)	0 (0)	1 (0.3)	1 (0.3)	Low
Wang R, 2020 [55]	Case series	China	ICU and non-ICU	125	Adults	56.8	15.2	4	0 (0)	1 (0.8)	9 (7)	9 (7)	Medium
Wang Y, 2020 [56]	Clinical trial	China	ICU and non-ICU	237	Adults	56	NR	21 (9)	14 (6)	NR	NR	NR	Medium
Wee, 2020 [57]	Prospective cohort	Singapore	ICU and non-ICU	3807	Adults	NR	NR	NR	1 (0.02)	3 (0.08)	NR	NR	Medium
Wu C, 2020 [58]	Retrospective cohort	China	ICU and non-ICU	201	Adults	63.7	26.4	67 (33)	44 (22)	1 (0.5)	0 (0)	0 (0)	Low
Xia, 2020 [59]	Case series	China	ICU and non-ICU	20	pediatric	65	NR	0 (0)	0 (0)	4 (0.2)	1 (5)	1 (5)	Medium
Yang X, 2020 [60]	Case series	China	ICU	710	Adults	67	100	37 (5)	32 (4)	0 (0)	4 (0.6)	4 (0.6)	Low
Yi, 2020 [61]	Case series	USA	ICU and non-ICU	132	Adult	62	50	5 (4)	1 (0.8)	NR	NR	NR	Medium
Zhang J, 2020 [62]	Case series	China	ICU and non-ICU	140	Adults	50.7	NR	NR	NR	2 (1)	1 (0.7)	1 (0.7)	Medium
Zhang G, 2020 [63]	Case series	China	ICU and non-ICU	221	Adults	48.9	80	26 (12)	5 (2)	2 (0.9)	6 (3)	6 (3)	Medium
Zhao, 2020 [64]	Case series	China	ICU and non-ICU	34	Adults	57.9	0	0 (0)	0 (0)	1 (3)	1 (3)	0 (0)	Medium
Zheng, 2020 [65]	Case series	China	ICU and non-ICU	1001	Adult and pediatric	NR	NR	NR	NR	2 (0.2)	NR	NR	Low
Zhou, 2020 [66]	Retrospective cohort	China	ICU and non-ICU	191	Adult	62	26	32 (17)	54 (28)	NR	NR	NR	Low
Zhu, 2020 [67]	Retrospective cohort	China	ICU and non-ICU	257	Adult and pediatric	53.7	1.16	0 (0)	NR	9 (3)	11 (4)	11 (4)	Low
Alvares P, 2020 [68]	Retrospective cohort	Brazil	ICU and non-ICU	32	Pediatric	59.3	9.3	2 (6)	1 (3)	1 (3)	1 (3)	NR	Medium
Borman, 2020 [69]	Case series	UK	ICU	719	Adults	NR	100.0	NR	NR	NR	NR	3NR	Low
Chauhdary W, 2020 [70]	Case series	Brunei Darussalam	ICU and non-ICU	141	Adults	NR		NR	NR	NR	7 (5)	NR	Low
Cheng L, 2020 [71]	Retrospective cohort	Hong Kong	ICU and non-ICU	147	Adults	85.0	3.0	NR	NR	NR	4 (3)	NR	Low

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Table 1. (Continued)

Study	Study design	Country	Setting	Number of patients	Age group of patients	Gender (% male)	ICU (%)	Patients who were ventilated n (%)	Patients who died n (%)	Viral co-infections n (%)	Bacterial co-infection n (%)	Fungal co-infections n (%)	Risk of bias
Cheng Y, 2020 [72]	Retrospective cohort	China	ICU and non-ICU	213	Adults	50.2		2 (1)	8 (4)	97 (46)	NR	NR	Low
Cheng K, 2020 [73]	Retrospective cohort	China	NR	212	Adults/Children	51.0		19 (9)	NR	NR	13 (6)	NR	Low
Contou D, 2020 [74]	Retrospective cohort	France	ICU	92	Adults	79.0	100.0	83 (90)	45 (49)	NR	32 (35)	NR	Low
Dupont D, 2020 [75]	Case series	France	ICU	19	Adults	78.0	100.0	18 (95)	NR	NR	NR	19 (100)	Low
Elabbadi A, 2020 [76]	Case series	France	ICU	101	Adults	78.2	100.0	83 (82)	21 (21)	NR	10 (10)	NR	Low
Falces-Romero, 2020 [77]	Retrospective cohort	Spain	ICU and non-ICU	10	Adults	80.0	70.0	7 (70)	7 (70)	NR	0	10 (100)	Medium
Falcone M, 2020 [78]	Prospective cohort	Italy	ICU and non-ICU	315	Adults	66.6	26.9	55 (17)	70 (22)	NR	11 (3)	2 (1)	Medium
Fu Y, 2020 [79]	Case series	China	ICU and non-ICU	5	Adults	80.0	100.0	5 (100)	NR	NR	5 (100)	2 (40)	Low
Garcia-Menino, 2021 [80]	Case series	Spain	ICU	7	Adults	86.0	100.0	NR	1 (14)	NR	7 (100)	NR	Low
Garcia-Vidal, 2021 [81]	Prospective cohort	Spain	ICU and non-ICU	989	Adults	55.8	15.0	NR	103 (10)	6 (1)	47 (5)	7 (1)	Low
Gouzien, 2020 [82]	Retrospective cohort	France	ICU	53	Adults	67.9	100.0	53 (100)	39 (74)	NR	NR	1 (2)	Medium
Hashemi S, 2020 [83]	Case series	Iran	ICU and non-ICU	105	Adults/Children	NR		NR	105 (100)	NR	NR	NR	Low
Hazra A, 2020 [84]	Retrospective cohort	USA	ICU and non-ICU	459	NR	NR		NR	NR	6 (1)	NR	NR	High
He Bing, 2020 [85]	Retrospective cohort	China	NR	21	Adults/Children	NR		NR	0	NR	2 (10)	4 (19)	Medium
Hirotsu Y, 2020 [86]	Prospective cohort	Japan	non-ICU	191	NR	NR		NR	NR	32 (17)	NR	NR	Medium
Hughes, 2020 [87]	Case series	UK	ICU	836	Adults	62.0	31.0	NR	262 (31)	NR	5 (1)	27 (3)	Low
Karaba, 2020 [88]	Retrospective cohort	USA	ICU and non-ICU	1016	Adults	54.0	12.0	NR	NR	2 NR	1NR	NR	Low
Kolenda, 2020 [89]	Prospective cohort	France	ICU	99	NR	NR	100.0	NR	NR	NR	17 (17)	NR	Low
Kumar, 2021 [90]	Retrospective cohort	USA	ICU and non-ICU	1573	Adults	57.9	31.0	247 (16)	413 (26)	NR	48 (3)	9 (1)	Low
Lardaro T, 2020 [91]	Retrospective cohort	USA	ICU and non-ICU	542	Adults	49.6	15.9	159 (29)	78 (14)	NR	8 (1)	NR	Medium
Lehmann C, 2020 [92]	Retrospective cohort	USA	ICU and non-ICU	321	Adults	48.0	5.0	NR	22 (7)	5 (2)	7 (2)	NR	Medium
Lendorf, 2020 [93]	Retrospective cohort	Denmark	ICU and non-ICU	115	Adults/Children	60.0	18.0	12 (10)	16 (14)	NR	9 (8)	1 (1)	Medium
Li J, 2020 [94]	Retrospective cohort	China	ICU and non-ICU	102	Adults/Children	66.7		NR	50 (49)	NR	159 (156)	NR	Medium
Li Z, 2020 [95]	Retrospective cohort	China	ICU and non-ICU	32	Adults	62.5	40.0	6 (19)	NR	6 (19)	10 (31)	2 (6)	High

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Table 1. (Continued)

Study	Study design	Country	Setting	Number of patients	Age group of patients	Gender (% male)	ICU (%)	Patients who were ventilated n (%)	Patients who died n (%)	Viral co-infections n (%)	Bacterial co-infection n (%)	Fungal co-infections n (%)	Risk of bias
Ma L, 2020 [96]	Retrospective cohort	China	ICU and non-ICU	250	Adults	46.0		5 (2)	4 (2)	4 (2)	2 (1)	NR	Low
Mahmoudi H, 2020 [97]	Cross-sectional study	Iran	ICU and non-ICU	342	Adults	NR		NR	NR	NR	6 (2)	NR	Medium
Mendes N, 2020 [98]	Retrospective cohort	USA	ICU and non-ICU	242	Adults	50.8		54 (22)	52 (21)	NR	6 (2)	NR	Low
Mughal, 2020 [99]	Restrospective cohort	USA	ICU and non-ICU	129	Adults	62.8	30.2	30 (23)	20 (16)	NR	NR	NR	Low
Nasir N, 2020 [100]	Retrospective cohort	Pakistan	ICU and non-ICU	30	Adults	83.0	33.0	24 (80)	7 (23)	NR	6 (20)	7 (23)	Low
Nasir N, 2020 [101]	Retrospective cohort	Pakistan	ICU and non-ICU	147	Adults	60.0			NR	NR	9 (6)	1 (1)	Medium
Ng K F, 2020 [102]	Case series	China	ICU and non-ICU	8	Pediatric	25.0	25.0	NR	NR	5 (63)	NR	NR	Low
Nori, 2021 [103]	Retrospective cohort	USA	ICU and non-ICU	152	Adults/Children	59.0	55.9	NR	86 (57)	NR	112 (74)	3 (2)	Low
Obata, 2020 [104]	Retrospective cohort	USA	ICU and non-ICU	226	Adults	55.1	24.8	NR	41 (18)	NR	8 (4)	8 (4)	Medium
Oliva, 2020 [105]	Case series	Italy	ICU and non-ICU	7	Adults	57.0	14.3	NR	NR	NR	7 (100)	NR	Low
Papamanoli, 2020 [106]	Retrospective cohort	USA	ICU and non-ICU	447	Adults	66.0	45.2	115 (26)	102 (23)	NR	NR	NR	Low
Peci A, 2021 [107]	Case-control	Canada	ICU and non-ICU	325	Adults/Children	NR		NR	NR	8 (2)	NR	NR	Low
Pereira, 2021 [108]	Case-control	New York	ICU and non-ICU	87	Adults	60.9	48.3	NR	32 (37)	10 (11)	6 (7)	1 (1)	Medium
Pettit, 2020 [109]	Retrospective cohort	USA	ICU and non-ICU	148	Adults	37.5	70.3	48 (32)	46 (31)	1 (1)	14 (9)	2 (1)	Low
Pickens, 2021 [110]	Retrospective cohort	Chicago	ICU	179	Adults	61.5	100.0	179 (100)	34 (19)	NR	28 (16)	NR	Low
Ramadan H, 2021 [111]	Prospective cohort	Egypt	ICU and non-ICU	260	Adults	55.4		8 (3)	24 (9)	NR	37 (14)	NR	Low
Reig S, 2020 [112]	Retrospective cohort	Germany	ICU and non-ICU	213	Adults	61.0	33.0	57 (27)	51 (24)	NR	26 (12)	6 (3)	Low
Ripa M, 2020 [113]	Prospective cohort	Italy	ICU and non-ICU	731	Adults	68.0	12.0	NR	194 (27)	NR	24 (3)	11 (2)	Low
Rothe K, 2020 [114]	Retrospective cohort	Germany	ICU and non-ICU	140	Adults	64.0	15.0	41 (29)	NR	NR	NR	9 (6)	Low
Segrelles-Calvo G, 2021 [115]	Case series	Spain	ICU and non-ICU	7	Adults	71.0	86.0	7 (100)	5 (71)	NR	NR	7 (100)	Low
Sharifipour E, 2020 [116]	Prospective cohort	Iran	ICU	19	Adults	58.0	100.0	19 (100)	18 (95)	NR	19 (100)	NR	Low
Sogaard, 2021 [117]	Retrospective cohort	Switzerland	ICU and non-ICU	162	Adults	61.1	25.3	NR	17 (10)	5 (3)	19 (12)	3 (2)	Low
Soriano, 2021 [118]	Retrospective cohort	Spain	ICU	83	Adults	79.0	100.0	78 (94)	20 (24)	NR	7 (8)	NR	Low
Tang, 2021 [119]	Retrospective cohort	China	NR	78	Adults/Children	53.0		NR	NR	4 (5)	5 (6)	NR	Low

(Continued)

Table 1. (Continued)

Study	Study design	Country	Setting	Number of patients	Age group of patients	Gender (% male)	ICU (%)	Patients who were ventilated n (%)	Patients who died n (%)	Viral co-infections n (%)	Bacterial co-infection n (%)	Fungal co-infections n (%)	Risk of bias
Torrego, 2020 [120]	Retrospective cohort	Spain	ICU	163	NR	NR	100.0	139 (85)	23 (14)	NR	18 (11)	NR	High
Townsend, 2020 [121]	Prospective cohort	Ireland	ICU and non-ICU	117	Adults	63.0	29.1	NR	17 (15)	NR	6 (5)	1 (1)	Low
Verroken, 2020 [122]	Prospective cohort	Belgium	ICU	32	NR	NR	100.0	NR	NR	NR	13 (41)	NR	Medium
Wang L, 2020 [123]	Retrospective cohort	UK	ICU and non-ICU	1396	Adults	65.0	30.0	NR	420 (30)	NR	11 (1)	NR	Low
Wei L, 2020 [124]	Retrospective cohort	China	non-ICU	43	Adults	0.0	0.0	NR	NR	NR	NR	NR	Low
White P, 2020 [125]	Retrospective cohort	UK	ICU and non-ICU	135	Adults	69.0		NR	51 (38)	NR	NR	36 (27)	Low
Wu Q, 2020 [126]	Retrospective cohort	China	NR	74	Pediatric	59.5		1 (1)	NR	10 (14)	16 (22)	NR	Low
Xia P, 2020 [127]	Retrospective cohort	China	ICU	81	Adults	66.7	100.0	66 (81)	60 (74)	NR	34 (42)	NR	Low
Xu J, 2020 [128]	Retrospective cohort	China	ICU	239	Adults	59.8	100.0	165 (69)	147 (62)	NR	25 (10)	NR	Low
Xu S, 2020 [129]	Retrospective cohort	China	ICU and non-ICU	64	Adults	0.0	1.6	NR	NR	9 (14)	10 (16)	NR	Low
Xu W, 2021 [130]	Retrospective cohort	China	ICU and non-ICU	659	Adults/Children	50.4	5.0	NR	NR	NR	48 (7)	NR	Low
Yao T, 2020 [131]	Retrospective cohort	China	NR	83	Adults	63.9		71 (86)	83 (100)	NR	36 (43)	NR	Low
Yu C, 2020 [132]	Retrospective cohort	China	NR	128	Adults	43.0		NR	14 (11)	64 (50)	5 (4)	NR	Low
Yue H, 2020 [133]	Retrospective cohort	China	NR	307	Adults	47.3		NR	NR	176 (57)	NR	NR	Medium
Yusuf E, 2021 [134]	Case-control	Netherlands	ICU	92	Adults	76.1	100.0	NR	NR	NR	NR	10 (11)	High
Zhang C, 2020 [135]	Retrospective cohort	China	NR	34	Pediatric	41.0		NR	NR	13 (38)	9 (26)	NR	Low
Zhang H, 2020 [136]	Retrospective cohort	China	NR	38	Adults	84.2		23 (61)	8 (21)	NR	37 (97)	3 (8)	Low

[a]ICU: intensive care unit.
[b]NR: Not reported.

https://doi.org/10.1371/journal.pone.0251170.t001
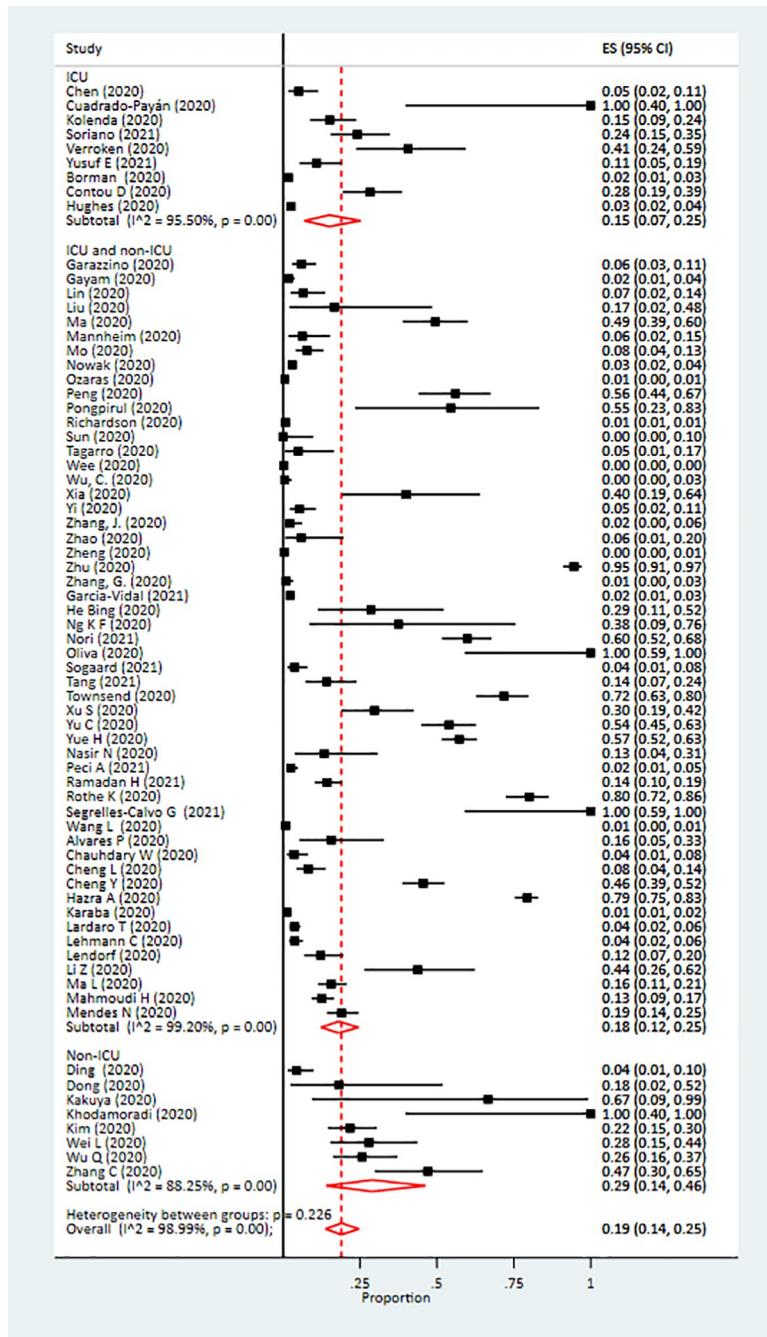
Fig 2. Forest plot of pooled prevalence of co-infection in patients infected with SARS-CoV-2.

https://doi.org/10.1371/journal.pone.0251170.g002

The overall prevalence of comorbidities was 42% (95% CI: 35%-49%). Among those with co-infections, the prevalence of comorbidities was 32% (95% CI: 24%-41%), while it was 54% (95% CI: 42%-65%) among those who were super-infected.

Patients with a co-infection or superinfection had a higher odds of dying than those who only had SARS-CoV-2 infection (odds ratio [OR] = 3.31, 95% CI: 1.82–5.99). Subgroup analysis of mortality showed similar results, where the odds of death was higher among patients who were co-infected (OR = 2.84; 95% CI: 1.42–5.66) and those who were super-infected
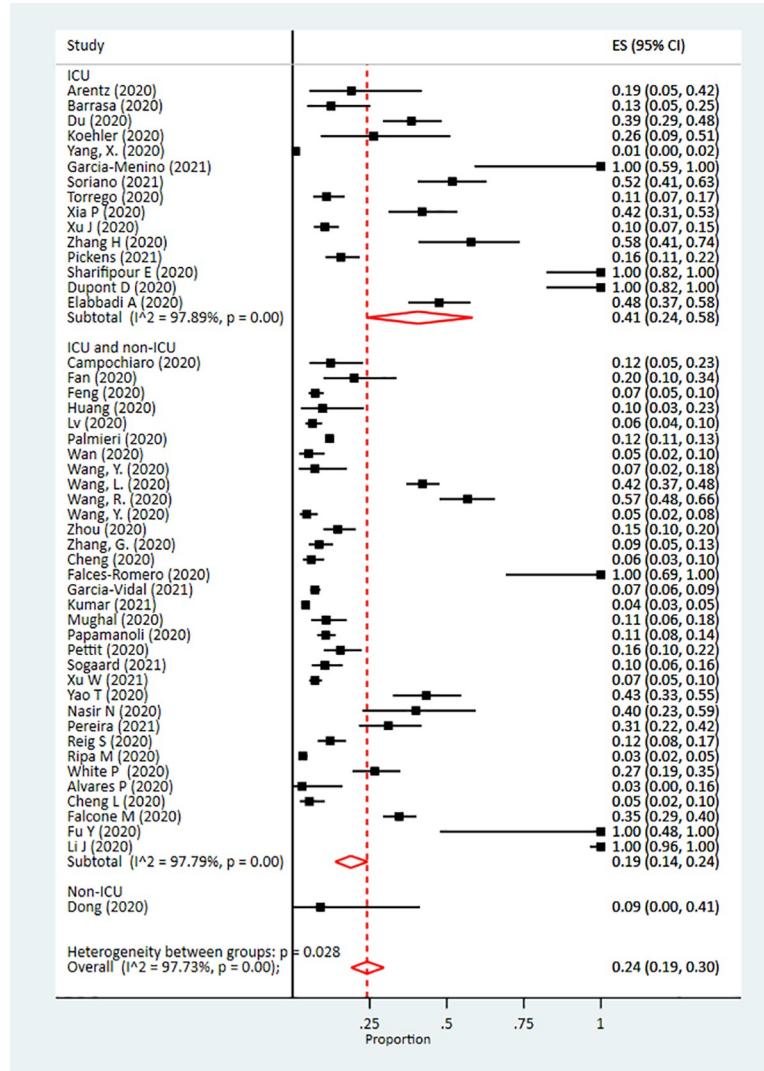
Fig 3. Forest plot of pooled prevalence of superinfection in patients infected with SARS-CoV-2.

https://doi.org/10.1371/journal.pone.0251170.g003

(OR = 3.54; 95% CI: 1.46–8.58). There was a higher prevalence of mechanical ventilation among patients with superinfections (45% [95% CI: 33%-58%]) compared to those with co-infections (10% [95% CI: 5%-16%]). Fifty studies reported data on average LOS. The average LOS for co-infected patients was 29 days (standard deviation [SD] = 6.7), while the average LOS for super-infected patients was 16 days (SD = 6.2). None of the studies included in this meta-analysis reported data on discharge disposition and readmissions.

Risk of bias assessment

Sixty-two percent (73/118) of studies were rated as having low risk of bias, 34% (40/118) as having medium risk of bias, and 4% (5/118) as having a high risk of bias.

Discussion

We found that 19% of patients with SARS-CoV-2 were co-infected with other pathogens, and the prevalence of co-infection was higher among patients who were not in the ICU (29%). We

Table 2. All identified organisms as a proportion of total number of organisms per pathogen.

Pathogen type	Co-infection (N = 1910) No. (%)	Superinfection (N = 480) No. (%)
Bacteria		
Staphylococcus aureus	148 (7.7)	13 (2.7)
Haemophilus influenza	127 (6.6)	6 (1.3)
Mycoplasma pneumoniae	82 (4.3)	6 (1.3)
Acinetobacter spps	78 (4.1)	107 (22.3)
Escherichia coli	73 (3.8)	33 (6.9)
Stenotrophomonas maltophilia	10 (0.5)	18 (3.8)
Klebsiella pneumoniae	189 (9.9)	28 (5.8)
Streptococcus pneumoniae	156 (8.2)	4 (0.8)
Chlamydia pneumoniae	29 (1.5)	0 (0)
Bordetella	3 (0.2)	0 (0)
Moraxella catarrhalis	32 (1.7)	2 (0.4)
Pseudomonas	67 (3.5)	52 (10.8)
Enterococcus faecium	14 (0.7)	22 (4.6)
Viruses		
Non-SARS-CoV-2[a] coronavirus strains	38 (2.0)	9 (1.9)
Human influenza A	426 (22.3)	0 (0)
Human influenza *B*	73 (3.8)	0 (0)
Respiratory syncytial virus	72 (3.8)	2 (0.4)
Parainfluenza	17 (0.9)	0 (0)
Human metapneumovirus	20 (1.0)	9 (1.9)
Rhinovirus	68 (3.6)	11 (2.3)
Adenovirus	35 (1.8)	2 (0.4)
Fungi		
Mucor	6 (0.3)	1 (0.2)
Candida spp.	19 (1.0)	90 (18.8)
Aspergillus	128 (6.7)	65 (13.5)

[a]SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

https://doi.org/10.1371/journal.pone.0251170.t002

also found a higher prevalence of superinfection compared to co-infection (24%), particularly among ICU patients (41%). Further, we found that super-infected patients had a higher prevalence of mechanical ventilation and comorbidities, and a higher risk of death.

Two previous reviews found a prevalence of bacterial co-infection of 7–8% and viral co-infection of 3% in SARS-CoV-2 infected patients, which are lower than our estimates [11, 12]. We extended this work by distinguishing between super- and co-infection because of the different implications of co-infections vs. superinfections. In particular, bacteria and other pathogens have been shown to complicate viral pneumonia and lead to poor outcomes [137]. In addition, our review spanned a longer period of time and included many newer studies, which may further account for differences in prevalence data.

The three most frequently identified bacteria among co-infected patients in our study were *Klebsiella pneumonia*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. *Streptococcus pneumoniae* is a frequent cause of superinfection in other respiratory infections, such as influenza [138]. A study by Zhu et al. showed similar results [67], and a review by Lansbury et al. showed that *Klebsiella pneumoniae* and *Haemophilus influenza* were some of the most frequent bacterial co-infecting pathogens [11]. As expected, *Staphylococcus aureus* also was present in a

sizeable number of cases. The most frequent bacteria identified in super-infected patients was *Acinetobacter spp.*, which is a common infection, especially in ventilated patients [139].

In our study, the three most frequently identified viruses among co-infected patients were influenza type A, influenza type B, and respiratory syncytial virus. These findings are important particularly for influenza because testing constraints continue to exist, yet clinical presentation of influenza and SARS-CoV-2 is similar. There are major infection control and clinical implications of missing a SARS-CoV-2 or influenza diagnosis if co-infection is not considered and diagnostic testing for both pathogens is not undertaken.

Our findings have implications for infection preventionists, clinicians, and laboratory leaders. Respiratory virus diagnostic testing protocols should take into account that co-infection with SARS-CoV-2 is not infrequent, and therefore viral panel testing may be advisable in patients with compatible symptoms. Treatment protocols should also include assessment for co-infections, particularly influenza, so that appropriate treatment for both SARS-CoV-2 and influenza can be administered.

Another key finding from our study was that co-infection or superinfection was associated with an increased odds of death. This is consistent with other studies that have shown a positive association between co-infection or superinfection and increased risk of death among patients with the SARS-CoV-2 infection [140, 141].

Our study showed that antibiotics were administered in 98% of the 83 studies that reported this data. The type of antibiotics (i.e., broad or narrow spectrum) were not widely ascertainable, as these details were not provided in many studies. In the spirit of antibiotic stewardship, antibiotic use even in SARS-CoV-2 infected patients should be judicious and only in cases with an objective diagnosis of bacterial co-infection.

Our study has limitations. We were not able to assess important outcomes, such as discharge disposition and hospital readmissions, due to a lack of these data in the included studies. We were also not able to document time to superinfection, as the included studies did not report this information. Studies provided the number of patients with superinfections without stating the exact time when this determination was made after SARS-CoV-2 diagnosis. Most of the studies included in the meta-analysis were case series with their inherent limitations [142]. It is possible that some of the pathogens that were reported as superinfections or secondary infections were present but not tested for at admission and hence were co-infections. It was not possible to assess this from the studies. There was significant heterogeneity in the studies, as was anticipated given the variation in settings, patient populations, and diagnostic testing platforms across the studies.

Conclusions

Our study showed that as many as 19% of patients with COVID-19 have co-infections and 24% have superinfections. The presence of either co-infection or superinfection was associated with poor outcomes, such as increased risk of mortality. Our findings support the need for diagnostic testing to identify and treat co-occurring respiratory infections among patients with SARS-CoV-2 infection.

Supporting information

S1 Fig. Forest plot of pooled prevalence of viral respiratory co-infections and viral superinfections in patients infected with SARS-CoV-2.
(TIF)

S2 Fig. Forest plot of pooled prevalence of bacterial co-infections and bacterial superinfections in patients infected with SARS-CoV-2.
(TIF)

S3 Fig. Forest plot of pooled prevalence of fungal co-infections and fungal superinfections in patients infected with SARS-CoV-2.
(TIF)

S1 File. Study protocol.
(PDF)

S2 File. Supplementary material: Search strategies, COVID-19 and co-infections, and final search.
(PDF)

S3 File. PRISMA 2009 checklist.
(PDF)

S4 File. Data used for the analysis.
(XLSX)

Author Contributions

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Writing – review & editing: Jackson S. Musuuza, Lauren Watson, Vishala Parmasad, Nathan Putman-Buehler, Leslie Christensen, Nasia Safdar.

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