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%, I² = 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 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 I² 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
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%).
| Study                  | Study design        | Country     | Setting                                      | Number 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                                          | 21 Adults 52       |                | 100      | 15 (52)                           | 3 (14)                  | 1 (50)                    | 0 (0)                         | 0 (0)         | Medium      |
| Barrasa, 2020 [23]    | Case series         | Spain       | ICU                                          | 48 Adults 56       |                | 100      | 45 (94)                           | 16 (33)                 | 6 (13)                    | 1 (2)                         | 4 (9)         | Low         |
| Campochiaro, 2020 [24]| Prospective cohort  | Italy       | ICU and non-ICU                              | 34 Adults 29       | Adult          | 67.9     | 5 (17)                            | 0 (0)                   | 0 (0)                      | 5 (10)                        | 35 (7)                    | Low         |
| Chen, 2020 [25]       | Case series         | China       | ICU                                          | 99 Adults 68       |                | 100      | 17 (17)                           | 11 (11)                 | 4 (4)                     | 1 (1)                         | 0 (0)         | Medium      |
| Cuadrado-Payan, 2020  | Case series         | Spain       | ICU                                          | 4 Adults 75        |                | 100      | 3 (75)                            | 1 (1)                   | 0 (0)                      | 1 (25)                        | 0 (0)         | High        |
| Ding, 2020 [27]       | Case series         | China       | Non-ICU                                      | NR Adults 0        |                | 75       | 0                                 | 0 (0)                   | 0 (0)                      | 5 (4)                         | 0 (0)         | Medium      |
| Dong, 2020 [28]       | Case series         | China       | ICU                                          | 11 Adults/children |                | 75       | 1 (9)                             | 0 (0)                   | 4 (36)                    | 0 (0)                         | 0 (0)         | Medium      |
| Du, 2020 [39]         | Case series         | China       | ICU                                          | 109 Adults 54      |                | 100      | 25 (46)                           | 12 (24)                 | 4 (7)                     | 3 (5)                         | 0 (0)         | Medium      |
| Fan, 2020 [30]        | Retrospective cohort| China       | ICU and non-ICU                              | 50 Adults 83       |                | 54       | 23 (60)                           | 15 (33)                 | 6 (13)                    | 4 (9)                         | 0 (0)         | Low         |
| Feng, 2020 [31]       | Case series         | China       | ICU and non-ICU                              | 476 Adults 56.9    |                | 100      | 26 (44)                           | 38 (68)                 | 35 (7)                    | 0 (0)                         | 0 (0)         | Medium      |
| Garazzino, 2020 [32]  | Retrospective cohort| Italy       | ICU and non-ICU                              | 168 Children 55.9  |                | 100      | 2 (1)                             | 0 (0)                   | 10 (6)                    | 0 (0)                         | 0 (0)         | Low         |
| Gayam, 2020 [33]      | Case series         | USA         | ICU and non-ICU                              | 350 Adults 33      |                | 100      | 2 (1)                             | 0 (0)                   | 1 (3)                     | 0 (0)                         | 0 (0)         | Medium      |
| Huang, 2020 [34]      | Case series         | China       | ICU and non-ICU                              | 788 Children/Adults|                | 32       | 18 (2)                            | 0 (0)                   | 6 (7)                     | 0 (0)                         | 0 (0)         | Medium      |
| Koehler, 2020 [38]    | Case series         | Germany     | ICU and non-ICU                              | 100 Adults 32      |                | 100      | 18 (57)                           | 0 (0)                   | 3 (9)                     | 1 (3)                         | 0 (0)         | Medium      |
| Lian, 2020 [39]       | Retrospective cohort| China       | ICU and non-ICU                              | 92 Adults 94       |                | 100      | 38 (42)                           | 0 (0)                   | 32 (35)                   | 0 (0)                         | 0 (0)         | Low         |
| Ma, 2020 [42]         | Retrospective cohort| China       | ICU and non-ICU                              | 93 Adults 55       |                | 100      | 44 (47)                           | 46 (49)                 | 3 (3)                     | 1 (1)                         | 0 (0)         | Medium      |
| Mannheim, 2020 [43]   | Case series         | Turkey      | ICU and non-ICU                              | 64 Adults 66       |                | 100      | 36 (55)                           | 22 (34)                 | 36 (56)                   | 0 (0)                         | 0 (0)         | Medium      |
| Mian, 2020 [44]       | Case series         | China       | ICU and non-ICU                              | 135 Adults 56      |                | 100      | 36 (23)                           | 22 (14)                 | 36 (23)                   | 0 (0)                         | 0 (0)         | Low         |
| Ortega, 2020 [45]     | Case series         | Spain       | ICU and non-ICU                              | 106 Adults 50      |                | 100      | 36 (36)                           | 0 (0)                   | 0 (0)                     | 6 (6)                         | 0 (0)         | Medium      |
| Palacios, 2020 [46]   | Case series         | Spain       | ICU and non-ICU                              | 90 Adults 40       |                | 100      | 36 (36)                           | 0 (0)                   | 0 (0)                     | 6 (6)                         | 0 (0)         | Medium      |
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-infections n (%) | Fungal co-infections n (%) | Risk of bias |
|------------------------|----------------------|------------------------|--------------------------|--------------------|-----------------------|-----------------|---------|----------------------------------|------------------------|--------------------------|--------------------------------|--------------------------|--------------|
| Peng, 2020 [47]        | Retrospective cohort | China                  | ICU and non-ICU          | 75                 | Children              | 58              | 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)                            | 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)                 | 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)                                  | 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)                            | 1 (2)                    | 1 (2)                    | 1 (3)                                  | Low          |             |
| Wang L, 2020 [54]      | Case series          | China                  | ICU and non-ICU          | 339                | Adults                | 49              | 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)                            | 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                              | 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                              | 2 (0.2)                   | NR                      | 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)                            | 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)                    | NR                                  | NR          | Medium      |
| Borman, 2020 [69]      | Case series          | UK                     | ICU                    | 719                | Adults                | NR              | 100.0   | NR                              | NR                      | NR                      | NR                                  | 3NR         | Low         |
| Chaudhary W, 2020 [70] | Case series          | Brunei Darussalam      | ICU and non-ICU          | 141                | Adults                | NR              | NR      | NR                              | 7 (5)                    | NR                      | NR                                  | Low         |             |
| Cheng L, 2020 [71]     | Retrospective cohort | Hong Kong              | ICU and non-ICU          | 147                | Adults                | 85.0             | 3.0     | NR                              | NR                      | 4 (3)                    | NR                                  | Low         |             |

(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-infections n (%) | Fungal co-infections n (%) | Risk of bias | Patients with super-infections n (%) | Table 1. (Continued) |
|-------|-------------|---------|---------|-------------------|----------------------|----------------|--------|-----------------------------------|----------------------------|------------------------|-----------------------------|------------------------|-------------|-------------------------------------|--------------------------|
| Cheng Y, 2020 [72] | Retrospective cohort | China | ICU and non-ICU | 213 Adults | 50.2 | Adults | 8 (4) | 19 (9) | NR | NR | NR | NR | Low | NR | 2 (1) |
| Cheng K, 2020 [73] | Retrospective cohort | China | NR | 212 Adults/Children | 51.0 | Adults | 19 (9) | 8 (4) | NR | NR | NR | NR | Low | NR | 10 (10) |
| Contou D, 2020 [74] | Retrospective cohort | France | ICU | 92 Adults | 78.0 | Adults | 2 (1) | 83 (90) | 45 (49) | NR | NR | NR | NR | Low | 1 (1) |
| Dupont D, 2020 [75] | Case series | France | ICU | 19 Adults | 76.0 | Adults | 19 (100) | 100.0 | NR | NR | NR | NR | Low | NR | 10 (100) |
| Elabbadi A, 2020 [76] | Case series | France | ICU | 101 Adults | 78.2 | Adults | 21 (21) | 83 (82) | 45 (49) | NR | NR | NR | NR | Low | 1 (1) |
| Falces-Romero, 2020 [77] | Retrospective cohort | Spain | ICU and non-ICU | 10 Adults | 80.0 | Adults | 2 (1) | 73 (70) | 45 (49) | NR | NR | NR | NR | Medium | 1 (1) |
| Falcone M, 2020 [78] | Prospective cohort | Italy | ICU and non-ICU | 315 Adults | 66.6 | Adults | 21 (21) | 55 (53) | 50 (50) | NR | NR | NR | NR | Medium | 1 (1) |
| Garcia-Menino, 2021 [80] | Case series | Spain | ICU | 989 Adults | 55.8 | Adults | 21 (21) | 103 (100) | 45 (45) | NR | NR | NR | NR | Medium | 1 (1) |
| Garcia-Vidal, 2021 [81] | Prospective cohort | Spain | ICU and non-ICU | 989 Adults | 55.8 | Adults | 21 (21) | 103 (100) | 45 (45) | NR | NR | NR | NR | Medium | 1 (1) |
| Gouzien, 2020 [82] | Retrospective cohort | France | ICU | 53 Adults | 67.9 | Adults | 21 (21) | 83 (90) | 45 (49) | NR | NR | NR | NR | Medium | 1 (1) |
| Hashemi S, 2020 [83] | Case series | Iran | ICU and non-ICU | 105 Adults/Children | 60.0 | Adults/Children | 21 (21) | 100.0 | NR | NR | NR | NR | Low | NR | 10 (100) |
| Hazra A, 2020 [84] | Retrospective cohort | USA | ICU and non-ICU | 459 Adults | 66.6 | Adults/Children | 21 (21) | 100.0 | NR | NR | NR | NR | Low | NR | 10 (100) |
| He Bing, 2020 [85] | Retrospective cohort | China | ICU and non-ICU | 21 Adults | 80.0 | Adults | 19 (100) | 100.0 | NR | NR | NR | NR | Low | NR | 10 (100) |
| Hirotsu Y, 2020 [86] | Prospective cohort | Japan | ICU and non-ICU | 105 Adults | 60.0 | Adults | 21 (21) | 100.0 | NR | NR | NR | NR | Low | NR | 10 (100) |
| Hughes, 2020 [87] | Case series | UK | ICU | 836 Adults | 62.0 | Adults | 21 (21) | 262 (31) | 50 (50) | NR | NR | NR | NR | Low | 1 (1) |
| Karaba, 2020 [88] | Retrospective cohort | USA | ICU and non-ICU | 1016 Adults | 54.0 | Adults | 21 (21) | 100.0 | NR | NR | NR | NR | Low | NR | 10 (100) |
| Kolenda, 2020 [89] | Prospective cohort | France | ICU | 99 Adults | 66.7 | Adults | 21 (21) | 100.0 | NR | NR | NR | NR | Low | NR | 10 (100) |
| Kumar, 2021 [90] | Retrospective cohort | USA | ICU and non-ICU | 100 Adults | 66.7 | Adults | 21 (21) | 100.0 | NR | NR | NR | NR | Low | NR | 10 (100) |
| Study | Setting | Type of Study | Country | ICU and non-ICU (n) | Number of Patients (n) | Age group of patients (%) | Gender (% male) | ICU (%) | Patients who were ventilated n (%) | Patients who died n (%) | Viral co-infections n (%) | Bacterial co-infections n (%) | Fungal co-infections n (%) | Risk of bias |
|-------|---------|--------------|---------|---------------------|-----------------------|--------------------------|----------------|--------|----------------------------------|----------------------|---------------------------|---------------------------|--------------------------|-----------|
| Ma L, 2020 [96] | ICU and non-ICU | Retrospective cohort | China | 250 | Adults | 46.0 | 5 (2) | 4 (2) | 4 (2) | 2 (1) | NR | Low |
| Mahmoudi H, 2020 [97] | ICU and non-ICU | Cross-sectional study | Iran | 342 | Adults | NR | NR | NR | NR | 6 (2) | NR | Medium |
| Mendes N, 2020 [98] | ICU and non-ICU | Retrospective cohort | USA | 242 | Adults | 50.8 | 54 (22) | 52 (21) | 20 (8) | NR | Low |
| Mughal, 2020 [99] | ICU and non-ICU | Retrospective cohort | USA | 129 | Adults | 62.8 | 30.2 | 30 (25) | 26 (21) | 7 (2) | NR | Low |
| Nasir N, 2020 [100] | ICU and non-ICU | Retrospective cohort | Pakistan | 30 | Adults | 81.0 | 31.0 | 30 (80) | 24 (73) | 6 (20) | 7 (23) | Low |
| Nasir N, 2020 [101] | ICU and non-ICU | Retrospective cohort | Pakistan | 147 | Adults | 60.0 | NR | NR | 9 (6) | 1 (1) | NR | Medium |
| Ng K F, 2020 [102] | ICU and non-ICU | Case series | China | 8 | Pediatric | 25.0 | 25.0 | NR | NR | 5 (63) | NR | Low |
| Nori, 2021 [103] | ICU and non-ICU | Retrospective cohort | USA | 152 | Adults | 50.0 | 55.7 | NR | 86 (57) | 41 (27) | NR | Medium |
| Papamanoli, 2020 [104] | ICU and non-ICU | Retrospective cohort | Greece | 447 | Adults | 66.0 | 45.2 | 46 (5) | 102 (23) | 32 (7) | NR | Low |
| Peci A, 2021 [105] | ICU and non-ICU | Case-control | Canada | 7 | Adults | 57.0 | 13.0 | 10 (15) | NR | NR | NR | Low |
| Pereira, 2020 [106] | ICU and non-ICU | Case series | USA | 265 | Adults | 57.0 | 13.0 | 10 (15) | NR | NR | NR | Low |
| Pickens, 2021 [107] | ICU and non-ICU | Retrospective cohort | USA | 152 | Adults | 50.0 | 45.2 | 46 (5) | 102 (23) | 32 (7) | NR | Low |
| Ramo R, 2021 [108] | ICU and non-ICU | Prospective cohort | Spain | 25 | Adults | 54.0 | 8.0 | 24 (96) | NR | NR | NR | Low |
| Reig S, 2021 [109] | ICU and non-ICU | Retrospective cohort | Spain | 83 | Adults | 54.0 | 8.0 | 24 (96) | NR | NR | NR | Low |
| Rinaldi, 2021 [110] | ICU and non-ICU | Prospective cohort | Italy | 3 | Adults | 50.0 | 100.0 | NR | NR | 10 (100) | NR | Low |
| Ramadan H, 2021 [111] | ICU and non-ICU | Prospective cohort | Egypt | 260 | Adults | 52.0 | 8.0 | 24 (96) | NR | NR | NR | Low |
| Reig S, 2021 [112] | ICU and non-ICU | Prospective cohort | Spain | 83 | Adults | 54.0 | 8.0 | 24 (96) | NR | NR | NR | Low |
| Tang 2021 [113] | ICU and non-ICU | Retrospective cohort | China | 78 | Adults | 55.0 | 3.0 | 10 (13) | NR | NR | NR | Low |

(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-infections n (%) | Fungal co-infections n (%) | Risk of bias |
|------------------------------|----------------|---------------|------------------------------|--------------------|-----------------------|----------------|---------|---------------------------------|------------------------|--------------------------|-------------------------------|---------------------------|--------------|
| Torrego, 2020 [120]         | Retrospective | Spain         | ICU                          | 163                | NR                    | NR             | 100.0   | 139 (85)                        | 23 (14)                | NR                       | 18 (11)                      | NR                        | High         |
| Townsend, 2020 [121]        | Prospective   | Ireland       | ICU and non-ICU              | 117                | Adults                | 63.0           | 29.1    | NR                             | 17 (15)                | NR                       | 6 (5)                        | 1 (1)                     | Low          |
| Verroken, 2020 [122]        | Prospective   | Belgium       | ICU                          | 32                 | NR                    | NR             | 100.0   | NR                             | NR                     | NR                       | 13 (41)                      | NR                        | Medium       |
| Wang L, 2020 [123]          | Retrospective | UK            | ICU and non-ICU              | 1396               | Adults                | 65.0           | 30.0    | NR                             | 420 (30)               | NR                       | 11 (1)                      | NR                        | Low          |
| Wei L, 2020 [124]           | Retrospective | China         | non-ICU                      | 43                 | Adults                | 0.0            | 0.0     | NR                             | NR                     | 15 (35)                  | NR                           | NR                        | Low          |
| White P, 2020 [125]         | Retrospective | UK            | ICU and non-ICU              | 135                | Adults                | 69.0           | NR      | 51 (38)                        | NR                     | NR                       | 36 (27)                      | NR                        | Low          |
| Wu Q, 2020 [126]            | Retrospective | China         | NR                           | 74                 | Pediatric            | 59.5           | 1 (1)   | NR                             | 10 (14)                | 16 (22)                  | NR                           | Low          |
| Xia P, 2020 [127]           | Retrospective | China         | ICU                          | 81                 | Adults                | 66.7           | 100.0   | 66 (81)                        | 60 (74)                | NR                       | 34 (42)                      | NR                        | Low          |
| Xu J, 2020 [128]            | Retrospective | China         | ICU                          | 239                | Adults                | 59.8           | 100.0   | 165 (69)                       | 147 (62)               | NR                       | 25 (10)                      | NR                        | Low          |
| Xu S, 2020 [129]            | Retrospective | China         | ICU and non-ICU              | 64                 | Adults                | 0.0            | 1.6     | NR                             | NR                     | 9 (14)                   | 10 (16)                      | NR                        | Low          |
| Xu W, 2021 [130]            | Retrospective | China         | ICU and non-ICU              | 659                | Adults/Children       | 50.4           | 5.0     | NR                             | NR                     | NR                       | 48 (7)                       | NR                        | Low          |
| Yao T, 2020 [131]           | Retrospective | China         | NR                           | 83                 | Adults                | 63.9           | 71 (86) | 83 (100)                       | NR                     | 36 (43)                  | NR                           | Low          |
| Yu C, 2020 [132]            | Retrospective | China         | NR                           | 128                | Adults                | 43.0           | NR      | 14 (11)                        | 64 (50)                | 5 (4)                    | NR                           | Low          |
| Yue H, 2020 [133]           | Retrospective | 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 | China         | NR                           | 34                 | Pediatric            | NR             | 41.0    | NR                             | 13 (38)                | 9 (26)                   | NR                           | Low          |
| Zhang H, 2020 [136]         | Retrospective | China         | NR                           | 38                 | Adults                | 84.2           | 23 (61) | 8 (21)                         | NR                     | 37 (97)                  | 3 (8)                        | Low          |

aICU: intensive care unit.
bNR: Not reported.

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Co-infections and super-infections in SARS-CoV-2 positive patients
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 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.
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
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 influenzae* were some of the most frequent bacterial co-infecting pathogens [11]. As expected, *Staphylococcus aureus* also was present in a

| 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 spp* | 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  |                                 |                                 |
| *Non-SARS-CoV-2* | 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) |

*SARS-CoV-2*: severe acute respiratory syndrome coronavirus 2.

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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)

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References
1. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): cases in US 2020 [Available from: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html.

2. The World Health Organization. Coronavirus disease (COVID-19) Pandemic 2020 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.

3. The World Health Organization. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations 2019 [Available from: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations.

4. Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. 2020. https://doi.org/10.1002/jmv.25748 PMID: 32134116

5. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med. 2020.
6. Chertow DS, Memoli MJ. Bacterial coinfection in influenza: a grand rounds review. JAMA. 2013; 309(3):275–82. https://doi.org/10.1001/jama.2012.194139 PMID: 23321766

7. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis. 2008; 198(7):962–70. https://doi.org/10.1086/591708 PMID: 18710327

8. Lin D, Liu Z, Zhang M, Hu Y, Yang Q, Guo J, et al. Co-infections of SARS-CoV-2 with multiple common respiratory pathogens in infected patients. Sci China Life Sci. 2020; 63(4):606–9. https://doi.org/10.1007/s11427-020-1668-5 PMID: 32170625

9. Nowak MD, Sordillo EM, Giltman MR, Paniz-Mondolfi AE. Co-infection in SARS-CoV-2 infected Patients: Where Are Influenza Virus and Rhinovirus/Enterovirus? Journal of Medical Virology. 2020. https://doi.org/10.1002/jmv.25953 PMID: 32352574

10. Wang M, Wu Q, Xu W, Qiao B, Wang J, Zheng H, et al. Clinical diagnosis of 8274 samples with 2019-novel coronavirus in Wuhan. medRxiv. 2020;2020.02.12.20022327.

11. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. The Journal of infection. 2020. https://doi.org/10.1016/j.jinf.2020.05.046 PMID: 32473235

12. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. Clinical Infectious Diseases. 2020. https://doi.org/10.1093/cid/ciaa530 PMID: 32358954

13. Garcia-Vidal C, Sanjuan G, Moreno-Garcia E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clinical Microbiology and Infection. https://doi.org/10.1016/j.cmi.2020.07.041 PMID: 32745596

14. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015; 4:1. https://doi.org/10.1186/2046-4053-4-1 PMID: 25554246

15. Musuza J, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. The prevalence and outcomes of co-infection with COVID-19 and other pathogens: a rapid systematic review and meta-analysis. PROSPERO 2020 CRD42020189763Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020189763.

16. Murad MH, Sultan S, Haftar S, Bazerbach F. Methodological quality and synthesis of case series and case reports. BMJ Evidence-Based Medicine. 2018; 23(2):60. https://doi.org/10.1136/bmjebm-2017-110853 PMID: 29420178

17. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998; 52(6):377–84. https://doi.org/10.1136/jech.52.6.377 PMID: 9764259

18. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014; 72(1):39. https://doi.org/10.1186/1742-7622-72-39 PMID: 25810908

19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3):177–88. https://doi.org/10.1016/0197-2456(86)90046-2 PMID: 3802833

20. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol. 2014; 67(8):897–903. https://doi.org/10.1016/j.jclinepi.2014.03.003 PMID: 24794697

21. Lin L. Graphical augmentations to sample-size-based funnel plot in meta-analysis. Res Synth Methods. 2019; 10(3):376–88. https://doi.org/10.1002/jrsm.1340 PMID: 30664834

22. Arentz M, Yim E, Klafl K, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. 2020; 323(16):1612–4. https://doi.org/10.1001/jama.2020.4326 PMID: 32191259

23. Barrasa H, Rello J, Tejada S, Martin A, Balazikszita G, Vinuesa C, et al. SARS-CoV-2 in Spanish Intensive Care Units: Early experience with 15-day survival in Vitoria. Anaesth Crit Care Pain Med. 2020. https://doi.org/10.1016/j.accpm.2020.04.001 PMID: 32278670

24. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. European Journal of Internal Medicine. 2020; 76:43–9. https://doi.org/10.1016/j.ejim.2020.05.021 PMID: 32482597

25. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507–13. https://doi.org/10.1016/S0140-6736(20)30211-7 PMID: 32007143
26. Cuadrado-Payán E, Montagud-Marrahí E, Torres-Elorza M, Bodro M, Blasco M, Poch E, et al. SARS-CoV-2 and influenza virus co-infection. The Lancet. 2020; 395(10236):e84. https://doi.org/10.1016/S0140-6736(20)31052-7 PMID: 32423586

27. Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. J Med Virol. 2020. https://doi.org/10.1002/jmv.25781 PMID: 32196707

28. Dong X, Cao YY, Lu XX, Zhang JJ, Du H, Yan YQ, et al. Eleven faces of coronavirus disease 2019. Allergy. 2020. https://doi.org/10.1111/all.14289 PMID: 32196678

29. Du RH, Liu LM, Yin W, Wang W, Guan LL, Yuan ML, et al. Hospitalization and Critical Care of 109 Decedents with COVID-19 Pneumonia in Wuhan, China. Ann Am Thorac Soc. 2020. https://doi.org/10.1513/annalsats.202003-225OC PMID: 32255382

30. Fan W, Yumin Z, Zhongfang W, Min X, Zhe S, Zhiqiang T, et al. Clinical characteristics of COVID-19 infection in chronic obstructive pulmonary disease: a multicenter, retrospective, observational study. Journal of Thoracic Disease. 2020; 12(5):1811–23. https://doi.org/10.21037/jtd-20-1914 PMID: 32642086

31. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. American Journal of Respiratory and Critical Care Medicine. 2020; 201(11):1380–8. https://doi.org/10.1164/rcrm.202002-044OC PMID: 32275452

32. Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Eurosurveillance: bulletin European sur les maladies transmissibles = European communicable disease bulletin. 2020; 25(18). https://doi.org/10.2807/1560-7917.ES.2020.25.18.2000600 PMID: 32400362

33. Gayam V, Konala VM, Naramala S, Garlapati PR, Merghani MA, Regmi N, et al. Presenting characteristics, comorbidities, and outcomes of patients coinfected with COVID-19 and Mycoplasma pneumoniae in the USA. Journal of Medical Virology. 2020.

34. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223):497–506. https://doi.org/10.1016/S0140-6736(20)30183-5 PMID: 31986264

35. Kakuya F, Okubo H, Fujiyasu H, Wakabayashi I, Syouji M, Kinebuchi T. The first pediatric patients with coronavirus disease 2019 (COVID-19) in Japan; The risk of co-infection with other respiratory viruses. Japanese journal of infectious diseases. 2020.

36. Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of coronavirus disease 2019 and influenza a: A report from Iran. Archives of Iranian Medicine. 2020; 23(4):239–43. https://doi.org/10.34172/aim.2020.04 PMID: 32271596

37. Kim D, Quinn J, Pinskby B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. JAMA. 2020; 323(20):2085–6. https://doi.org/10.1001/jama.2020.6266 PMID: 32293646

38. Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenuer DA, Fuchs F, et al. COVID-19 associated pulmonary aspergillosis. Mycoses. 2020; 63(6):528–34. https://doi.org/10.1111/myc.13096 PMID: 32339396

39. Lian J, Jin X, Hao S, Cai H, Zhang S, Zheng L, et al. Analysis of Epidemiological and Clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan. Clinical Infectious Diseases. 2020.

40. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020; 63(3):364–74. https://doi.org/10.1007/s11427-020-1643-6 PMID: 32048163

41. Lv Z, Cheng S, Le J, Huang J, Feng L, Zhang B, et al. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. Microbes Infect. 2020. https://doi.org/10.1016/j.micinf.2020.05.007 PMID: 32425649

42. Ma S, Lai X, Chen Z, Tu S, Qin K. Clinical Characteristics of Critically Ill Patients Co-infected with SARS-CoV-2 and the Influenza Virus in Wuhan, China. International Journal of Infectious Diseases. 2020. https://doi.org/10.1016/j.ijid.2020.05.066 PMID: 32470606

43. Mannheim J, Gretsch S, Layden JE, Frichione MJ. Characteristics of Hospitalized Pediatric COVID-19 Cases—Chicago, Illinois, March—April 2020. J Pediatric Infect Dis Soc. 2020.

44. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clinical Infectious Diseases. 2020. https://doi.org/10.1093/cid/ciaa270 PMID: 32173725

45. Ozaras R, Cirpin R, Duran A, Duman H, Arslan O, Bakcan Y, et al. Influenza and COVID-19 Co-infection: Report of 6 cases and review of the Literature. Journal of Medical Virology. 2020.
Co-infections and super-infections in SARS-CoV-2 positive patients

46. Palmieri L, Vanacore N, Donfrancesco C, Lo Noce C, Canevelli M, Punzo O, et al. Clinical Characteristics of Hospitalized Individuals Dying with COVID-19 by Age Group in Italy. Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2020. https://doi.org/10.1093/gerona/glaa140 PMID: 32662813

47. Peng H, Gao P, Xu Q, Liu M, Peng J, Wang Y, et al. Coronavirus disease 2019 in children: Characteristics, antimicrobial treatment, and outcomes. Journal of Clinical Virology. 2020; 128.

48. Pongpirul WA, Mott JA, Woodring JV, Uyeki TM, MacArthur JR, Vachiraphan A, et al. Clinical Characteristics of Patients Hospitalized with Coronavirus Disease, Thailand. Emerging Infectious Diseases. 2020; 26(7).

49. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. Jama. 2020; 323(20):2052–9. https://doi.org/10.1001/jama.2020.6775 PMID: 32320003

50. Sun D, Chen X, Li H, Lu XX, Xiao H, Zhang FR, et al. SARS-CoV-2 infection in infants under 1 year of age in Wuhan City, China. World Journal of Pediatrics. 2020;1–7. https://doi.org/10.1007/s12519-020-00368-y PMID: 32504360

51. Tagarro A, Epalza C, Santos M, Sanz-Santaeufemia FJ, Otheo E, Moraleda C, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain. JAMA Pediatrics. 2020. https://doi.org/10.1001/jamapediatrics.2020.1346 PMID: 32267485

52. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. Journal of Medical Virology. 2020; 92(7):797–806. https://doi.org/10.1002/jmv.25783 PMID: 32198776

53. Wang Y, Liu Y, Liu L, Wang X, Luo N, Li L. Clinical Outcomes in 55 Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Who Were Asymptomatic at Hospital Admission in Shenzhen, China. Journal of Infectious Diseases. 2020; 221(11):1770–4. https://doi.org/10.1093/infdis/jiaa119 PMID: 32179910

54. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020; 80(6):639–45.

55. Wang R, Pan M, Zhang X, Han M, Fan X,Zhao F, et al. Epidemiological and clinical features of 125 Hospitalized Patients with COVID-19 in Fuyang, Anhui, China. International Journal of Infectious Diseases. 2020; 95:421–8. https://doi.org/10.1016/j.ijid.2020.03.070 PMID: 32289565

56. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020; 395(10236):1569–78. https://doi.org/10.1016/S0140-6736(20)31022-9 PMID: 3243584

57. Wee LE, Ko KKK, Ho WQ, Kwek GTC, Tan TT, Wijaya L. Community-acquired viral respiratory infections amongst hospitalized inpatients during a COVID-19 outbreak in Singapore: co-infection and clinical outcomes. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. 2020; 128:104436. https://doi.org/10.1016/j.jcv.2020.104436 PMID: 32472256

58. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020. https://doi.org/10.1001/jama.2020.6775 PMID: 32167524

59. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatric Pulmonology. 2020; 55(5):1169–74. https://doi.org/10.1002/ppul.24718 PMID: 32134205

60. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5):475–81. https://doi.org/10.1016/S2213-2600(20)30079-5 PMID: 32105632

61. Yi SG, Rogers AW, Saharia A, Aoun M, Faour R, Abdelrahim M, et al. Early Experience With COVID-19 and Solid Organ Transplantation at a US High-volume Transplant Center. Transplantation. 2020.

62. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020. https://doi.org/10.1111/all.14238 PMID: 32077115

63. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. 2020; 127:104364. https://doi.org/10.1016/j.jcv.2020.104364 PMID: 32311650

64. Zhao D, Yao F, Wang L, Zheng L, Gao Y, Ye J, et al. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. Clinical Infectious Diseases. 2020. https://doi.org/10.1093/cid/ciaa247 PMID: 32161968
65. Zheng X, Wang H, Su Z, Li W, Yang D, Deng F, et al. Co-infection of SARS-CoV-2 and Influenza virus in Early Stage of the COVID-19 Epidemic in Wuhan, China. Journal of Infection. 2020. https://doi.org/10.1016/j.jinf.2020.05.041 PMID: 32474045

66. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3 PMID: 32171076

67. Zhu X, Ge Y, Wu T, Zhao K, Shen Y, Wu B, et al. Co-infection with respiratory pathogens among COVID-2019 cases. Virus Research. 2020; 285. https://doi.org/10.1016/j.virusres.2020.198005 PMID: 32408156

68. Alvares PA. SARS-COV-2 AND RESPIRATORY SYNCTIAL VIRUS COINFECTION IN HOSPITALIZED PEDIATRIC PATIENTS. Pediatric Infectious Disease Journal. 2021. https://doi.org/10.1097/INF.0000000000003057 PMID: 33464015

69. Borman AM, Palmer MD, Fraser M, Patterson Z, Mann C, Oliver D, et al. COVID-19-Associated Invasive Aspergillosis: Data from the UK National Mycology Reference Laboratory. Journal of Clinical Microbiology. 2020; 59(1). https://doi.org/10.1128/JCM.02136-20 PMID: 33087440

70. Chauhdary WA, Chong PL, Mani BI, Asli R, Momin RN, Abdullah MS, et al. Primary Respiratory Bacterial Coinfections in Patients with COVID-19. The American journal of tropical medicine and hygiene. 2020; 103(2):917–9. https://doi.org/10.4269/ajtmh.20-0498 PMID: 32500854

71. Cheng LS, Chau SK, Tso EY, Tsang SW, Li IY, Wong BK, et al. Bacterial co-infections and antibiotic prescribing practice in adults with COVID-19: experience from a single hospital cluster. Ther Adv Infect Dis. 2020; 7:2049936120978095. https://doi.org/10.1177/2049936120978095 PMID: 33355724

72. Cheng Y, Ma J, Wang H, Wang X, Hu Z, Li H, et al. Co-infection of influenza A virus and SARS-CoV-2: A retrospective cohort study. Journal of Medical Virology. 2021. https://doi.org/10.1002/jmv.26817 PMID: 33475159

73. Cheng K, He M, Shu Q, Wu M, Chen C, Xue Y. Analysis of the Risk Factors for Nosocomial Bacterial Infection in Patients with COVID-19 in a Tertiary Hospital. Risk Management and Healthcare Policy. 2020; 13:2593–9. https://doi.org/10.2147/RMHP.S227963 PMID: 33223859

74. Contou D, Claudinon A, Pajot O, Micaelo M, Longuef Flandre P, Dubert M, et al. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Annals of intensive care. 2020; 10(1):119. https://doi.org/10.1186/s13613-020-00736-x PMID: 32894364

75. Dupont D, Menotti J, Turc J, Miossec C, Wallet F, Richard JC, et al. Pulmonary aspergillosis in critically ill patients with Coronavirus Disease 2019 (COVID-19). Medical Mycology. 2021; 59(1):110–4. https://doi.org/10.1093/mmy/myaa078 PMID: 32914189

76. Elabbadi A, Turpin M, Gerotzi afas GT, Teulier M, Voiriot G, Fartoukh M. Bacterial coinfection in critically ill COVID-19 patients with severe pneumonia. Infection. 2021. https://doi.org/10.1007/s15010-020-01553-x PMID: 33393065

77. Falces-Romero I, Ruiz-Bastian M, Diaz-Pollan B, Maseda E, Garcia-Rodriguez J. Isolation of Aspergillus spp. in respiratory samples of patients with COVID-19 in a Spanish Tertiary Care Hospital. Mycoses. 2020.

78. Falcone M, Tiseo G, Giordano C, Leonildi A, Menichini M, Vecchione A, et al. Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: a prospective observational study. Journal of Antimicrobial Chemotherapy. 2020.

79. Fu Y, Yang Q, Xu M, Kong H, Chen H, Fu Y, et al. Secondary Bacterial Infections in Critical Ill Patients With Coronavirus Disease 2019. Open Forum Infect Dis. 2020; 7(6):ofaa220. https://doi.org/10.1093/ofid/ofaa220 PMID: 32613024

80. Garcia-Menino I, Forcelledo L, Rosete Y, Garcia-Prieto E, Escudero D, Fernandez J. Spread of OXA-48-producing Klebsiella pneumoniae among COVID-19-infected patients: The storm after the storm. Journal of infection and public health. 2021; 14(1):50–2. https://doi.org/10.1016/j.jiph.2020.11.001 PMID: 33341484

81. Garcia-Vidal C, Sanjuan G, Moreno-Garcia E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2021; 27(1):83–8. https://doi.org/10.1016/j.cmi.2020.07.041 PMID: 32745996

82. Gouzien L, Cocherie T, Eloy O, Legriel S, Bedos JP, Simon C, et al. Invasive Aspergillosis Associated with severe COVID-19: A Word of Caution. Infect Dis Now. 2021. https://doi.org/10.1016/j.jdnow.2020.12.006 PMID: 33490993

83. Hashemi SA, Safamanesh S, Ghasemzadeh-Moghaddam H, Ghafouri M, Azimian A. High prevalence of SARS-CoV-2 and influenza A virus (H1N1) coinfection in dead patients in Northeastern Iran. Journal of Medical Virology. 2021; 93(2):1008–12. https://doi.org/10.1002/jmv.26364 PMID: 32720703
84. Hazra A, Collison M, Pisano J, Kumar M, Oehler C, Ridgway JP. Coinfections with SARS-CoV-2 and other respiratory pathogens. Infect Control Hosp Epidemiol. 2020; 41(10):1228–9. https://doi.org/10.1017/ice.2020.322 PMID: 32616098

85. He B, Wang J, Wang Y, Zhao J, Huang J, Tian Y, et al. The Metabolic Changes and Immune Profiles in Patients With COVID-19. Frontiers in Immunology. 2020; 11:2075. https://doi.org/10.3389/fimmu.2020.02075 PMID: 32983157

86. Hirotsu Y, Maejima M, Shibusawa M, Amemiya K, Nagakubo Y, Hosaka K, et al. Analysis of Covid-19 and non-Covid-19 viruses, including influenza viruses, to determine the influence of intensive preventive measures in Japan. Journal of Clinical Virology. 2020; 129:104543. https://doi.org/10.1016/j.jcv.2020.104543 PMID: 32663787

87. Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clinical Microbiology and Infection. 2020; 26(10):1395–9. https://doi.org/10.1016/j.cmi.2020.06.025 PMID: 32603803

88. Karaba SM, Jones G, Helsel T, Smith LL, Avery R, Dzintars K, et al. Prevalence of Co-infection at the Time of Hospital Admission in COVID-19 Patients, A Multicenter Study. Open Forum Infect Dis. 2021; 8(1):ofaa578. https://doi.org/10.1093/ofid/ofaa578 PMID: 33447639

89. Kolenda C, Ranc AG, Boisset S, Caspar Y, Carriego A, Souche A, et al. Assessment of Respiratory Bacterial Coinfections Among Severe Acute Respiratory Syndrome Coronavirus 2-Positive Patients Hospitalized in Intensive Care Units Using Conventional Culture and BioFire, FilmArray Pneumonia Panel Plus Assay. Open Forum Infect Dis. 2020; 7(11):ofaa484. https://doi.org/10.1093/ofid/ofaa484 PMID: 33204762

90. Kumar G, Adams A, Hererra M, Rojas ER, Singh V, Sakhuja A, et al. Predictors and outcomes of healthcare-associated infections in COVID-19 patients. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases. 2021; 104:287–92. https://doi.org/10.1016/j.ijid.2020.11.135 PMID: 33207271

91. Lardaro T, Wang AZ, Bucca A, Croft A, Glover N, Holt DB, et al. Characteristics of COVID-19 Patients with Bacterial Co-infection Admitted to the Hospital from the Emergency Department in a Large Regional Healthcare System. Journal of Medical Virology. 2021.

92. Lehmann CJ, Pho MT, Pitra D, Ridgway JP, Pettit NN. Community Acquired Co-infection in COVID-19: A Retrospective Observational Experience. Clinical Infectious Diseases. 2020.

93. Lendorf ME, Boisen MK, Kristensen PL, Lokkegaard ECL, Krog SM, Brandi L, et al. Characteristics and early outcomes of patients hospitalised for COVID-19 in North Zealand, Denmark. Dan Med J. 2020; 67(9). PMID: 32800073

94. Li J, Wang J, Yang Y, Cai P, Cao J, Cai X, et al. Etiology and antimicrobial resistance of secondary bacterial infections in patients hospitalised with COVID-19 in Wuhan, China: a retrospective analysis. Antimicrobial resistance and infection control. 2020; 9(1):153. https://doi.org/10.1186/s13756-020-00819-1 PMID: 32962731

95. Li Z, Chen ZM, Chen LD, Zhan YQ, Li SQ, Cheng J, et al. Coinfection with SARS-CoV-2 and other respiratory pathogens in patients with COVID-19 in Guangzhou, China. J Med Virol. 2020; 92(11):2381–3. https://doi.org/10.1002/jmv.26073 PMID: 32462695

96. Ma L, Wang W, Le Grange JM, Wang X, Du S, Li C, et al. Coinfection of SARS-CoV-2 and Other Respiratory Pathogens. Infect Drug Resist. 2020; 13:3045–53. https://doi.org/10.2147/IDR.S267238 PMID: 32922049

97. Mahmoudi H. Bacterial co-infections and antibiotic resistance in patients with COVID-19. GMS hygiene and infection control. 2020; 15:Doc35. https://doi.org/10.3205/dghk000370 PMID: 33391970

98. Goncalves Mendes Neto A, Lo KB, Watato A, Saiacup G, Pelayo J, DeJoy R, 3rd, et al. Bacterial infections and patterns of antibiotic use in patients with COVID-19. J Med Virol. 2021; 93(3):1489–95. https://doi.org/10.1002/jmv.26441 PMID: 32808695

99. Mughal MS, Kaur IP, Jaffrey AR, Dalmacion DL, Wang C, Koyoda S, et al. COVID-19 patients in a tertiary US hospital: Assessment of clinical course and predictors of the disease severity. Respir Med. 2020; 172:106130. https://doi.org/10.1016/j.rmed.2020.106130 PMID: 32896798

100. Nasir N, Mahmood F, Habib K, Khanum I, Jamil B. Tocilizumab for COVID-19 Acute Respiratory Distress Syndrome: Outcomes Assessment Using the WHO Ordinal Scale. Cureus. 2020; 12(12):e12290. https://doi.org/10.7759/cureus.12290 PMID: 33510889

101. Nasir N, Farooqi J, Mahmood SF, Jabeen K. COVID-19-associated pulmonary aspergillosis (CAPA) in patients admitted with severe COVID-19 pneumonia: An observational study from Pakistan. Mycoses. 2020; 63(8):766–70. https://doi.org/10.1111/myc.13135 PMID: 32585069
102. Ng KF, Bandi S, Bird PW, Wei-Tze Tang J. COVID-19 in Neonates and Infants: Progression and Recovery. Pediatric Infectious Disease Journal. 2020; 39(7):e140–e2. https://doi.org/10.1097/INF.0000000000002738 PMID: 32384398

103. Nori P, Cowman K, Chen V, Bartash R, Szymczak W, Madaline T, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. Infection Control and Hospital Epidemiology. 2021; 42(1):84–8. https://doi.org/10.1017/ice.2020.368 PMID: 32703320

104. Obata R, Maeda T, Do DR, Kuno T. Increased secondary infection in COVID-19 patients treated with steroids in New York City. Japanese journal of infectious diseases. 2020. https://doi.org/10.7883/yoken.JJD.2020.884 PMID: 33390434

105. Oliva A, Siccardi G, Migliarini A, Cancellini F, Carnevalini M, D’Andria M, et al. Co-infection of SARS-CoV-2 with Chlamydia or Mycoplasma pneumoniae: a case series and review of the literature. Infection. 2020; 48(6):871–7. https://doi.org/10.1007/s10152-020-01483-8 PMID: 32725598

106. Papamanoli A, Yoo J, Grewal P, Predun W, Hotelling J, Jacob R, et al. High-dose methylprednisolone in nonintubated patients with severe COVID-19 pneumonia. European journal of clinical investigation. 2021; 51(2):e13458. https://doi.org/10.1111/eji.13458 PMID: 33219551

107. Peci A, Tran V, Guthrie JL, Li Y, Nelson P, Schwartz KL, et al. Prevalence of Co-Infections with Respiratory Viruses in Individuals Investigated for SARS-CoV-2 in Ontario, Canada. Viruses. 2021; 13(1). https://doi.org/10.3390/v13010130 PMID: 33477649

108. Pereira MR, Aversa MM, Farr MA, Aaron JG, Mohan S, et al. Tocilizumab for severe COVID-19 in solid organ transplant recipients: a matched cohort study. American Journal of Transplantation. 2020; 20(11):3198–205. https://doi.org/10.1111/ajt.16314 PMID: 32946668

109. Pettit NN, Nguyen CT, Mullet GM, Wu D, Kimmig L, Pitrak D, et al. Late onset infectious complications and safety of tocilizumab in the management of COVID-19. J Med Virol. 2021; 93(3):1459–64. https://doi.org/10.1002/jmv.26429 PMID: 32790075

110. Pickens CO, Gao CA, Cuttica M, Smith SB, Pesce L, Grant R, et al. Bacterial superinfection pneumonia in SARS-CoV-2 respiratory failure. medRxiv. 2021. https://doi.org/10.1101/2021.01.12.20248588 PMID: 33469593

111. Ramadan HK, Mahmoud MA, Aburahma MZ, Eikhawaga AA, El-Mokhtar MA, Sayed IM, et al. Predictors of Severity and Co-Infection Resistance Profile in COVID-19 Patients: First Report from Upper Egypt. Infect Drug Resist. 2020; 13:3409–22. https://doi.org/10.2147/IDR.S272605 PMID: 33116660

112. Rieg S, von Cube M, Kalbhenn J, Utolzino S, Pernice K, Bechet L, et al. COVID-19 in-hospital mortality and mode of death in a dynamic and non-restricted tertiary care model in Germany. PloS one. 2020; 15(11):e0242127. https://doi.org/10.1371/journal.pone.0242127 PMID: 33180830

113. Ripa M, Galli L, Poli A, Oltolini C, Spagnuolo V, Mastrangelo A, et al. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. Clinical Microbiology and Infection. 2020. https://doi.org/10.1016/j.cmi.2020.10.021 PMID: 33223114

114. Rothe K, Feihl S, Schneider J, Wallnofer F, Wurst M, Lukas M, et al. Rates of bacterial co-infections and antimicrobial use in COVID-19 patients: a retrospective cohort study in light of antibiotic stewardship. Eur J Clin Microbiol Infect Dis. 2021; 40(4):859–69. https://doi.org/10.1007/s10096-020-04063-8 PMID: 33140176

115. Segrelles-Calvo G, Araujo GRS, Llopis-Pastor E, Carrillo J, Hernandez-Hernandez M, Rey L, et al. Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia. Mycoses. 2021; 64(2):144–51. https://doi.org/10.1111/myc.13219 PMID: 33217071

116. Sharlifpour E, Shams S, Esmkhani M, Khoddadi J, Fotouhi-Ardakani R, Koohpaei A, et al. Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. BMC infectious diseases. 2020. https://doi.org/10.1186/s12879-020-05374-z PMID: 32873235

117. Sogaard KK, Baetig V, Ostoff M, Marsch S, Leuzing K, Schweitzer M, et al. Community-acquired and hospital-acquired respiratory tract infection and bloodstream infection in patients hospitalized with COVID-19 pneumonia. J Intensive Care. 2021; 9(1):10. https://doi.org/10.1186/s40560-021-00526-y PMID: 33461613

118. Soriano MC, Vaquero C, Ortiz-Fernandez A, Caballero A, Blandino-Ortiz A, de Pablo R. Low incidence of co-infection, but high incidence of ICU-acquired infections in critically ill patients with COVID-19. The Journal of infection. 2021; 82(2):e20–e61. https://doi.org/10.1016/j.jinf.2020.09.010 PMID: 32956729

119. Tang ML, Li YQ, Chen X, Lin H, Jiang ZC, Gu DL, et al. Co-Infection with Common Respiratory Pathogens and SARS-CoV-2 in Patients with COVID-19 Pneumonia and Laboratory Biochemistry Findings: A Retrospective Cross-Sectional Study of 78 Patients from a Single Center in China. Med Sci Monit. 2021; 27:e929783. https://doi.org/10.12659/MSM.929783 PMID: 33388738
120. Torrego A, Pajares V, Fernandez-Arias C, Vera P, Mancebo J. Bronchoscopy in Patients with COVID-19 with Invasive Mechanical Ventilation: A Single-Center Experience. Am J Respir Crit Care Med. 2020; 202(2):284–7. https://doi.org/10.1164/ajrccm.202004-0945LE PMID: 32412787

121. Townsend L, Hughes G, Kerr C, Kelly M, O'Connell R, Sweeney E, et al. Bacterial pneumonia coinfection and antimicrobial therapy duration in SARS-CoV-2 (COVID-19) infection. JAC Antimicrob Resist. 2020; 2(3):diaa071. https://doi.org/10.1093/jac/diaa071 PMID: 32864608

122. Verroken A, Scohy A, Gerard L, Wittebole X, Collienne C, Laterre PF. Coinfections in COVID-19 critically ill and antibiotic management: a prospective cohort analysis. Crit Care. 2020; 24(1):410. https://doi.org/10.1186/s13054-020-03135-7 PMID: 32646494

123. Wang L, Amin AK, Khanna P, Aali A, McGregor A, Bassett P, et al. An observational cohort study of bacterial co-infection and implications for empirical antibiotic therapy in patients presenting with COVID-19 to hospitals in North West London. Journal of Antimicrobial Chemotherapy. 2020.

124. Wei L, Gao X, Chen S, Zeng W, Wu J, Lin X, et al. Clinical Characteristics and Outcomes of Bearb-Age Women With COVID-19 in Wuhan: Retrospective, Single-Center Study. Journal of Medical Internet Research. 2020; 22(8):e19642. https://doi.org/10.2196/19642 PMID: 32750000

125. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clinical Infectious Diseases. 2020. https://doi.org/10.1093/cid/ciaa1298 PMID: 32860682

126. Xu W, Sun NN, Gao HN, Chen ZY, Yang Y, Ju B, et al. Risk factors analysis of COVID-19 patients with ARDS and prediction based on machine learning. Scientific reports. 2021; 11(1):2933. https://doi.org/10.1038/s41598-021-82492-x PMID: 33536460

127. Xia P, Wen Y, Duan Y, Su H, Cao W, Xiao M, et al. Clinicopathological Features and Outcomes of Acute Kidney Injury in Critically Ill COVID-19 with Prolonged Disease Course: A Retrospective Cohort. J Am Soc Nephrol. 2020; 31(9):2205–21. https://doi.org/10.1681/ASN.2020040426 PMID: 32623262

128. Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. Crit Care. 2020; 24(1):394. https://doi.org/10.1186/s13054-020-03098-9 PMID: 32631393

129. Xu S, Shao F, Bao B, Ma X, Xu Z, You J, et al. Clinical Manifestation and Neonatal Outcomes of Pregnant Women With Coronavirus Disease 2019 Pneumonia in Wuhan, China. Open Forum Infect Dis. 2020; 7(7):ofaa283. https://doi.org/10.1093/ofid/ofaa283 PMID: 32743014

130. Xu W, Sun NN, Gao HN, Chen ZY, Yang Y, Ju B, et al. Risk factors analysis of COVID-19 patients with ARDS and prediction based on machine learning. Scientific reports. 2021; 11(1):2933. https://doi.org/10.1038/s41598-021-82492-x PMID: 33536460

131. Yao T, Gao Y, Cui Q, Peng B, Chen Y, Li J, et al. Clinical characteristics of a group of deaths with COVID-19 pneumonia in Wuhan, China: a retrospective case series. BMC infectious diseases. 2020; 20(1):695. https://doi.org/10.1186/s12879-020-05423-7 PMID: 32692639

132. Yu C, Zhang Z, Guo Y, Shi J, Pei G, Yao Y, et al. Lopinavir/ritonavir is associated with pneumonia resolution in COVID-19 patients with influenza coinfection: A retrospective matched-pair cohort study. J Med Virol. 2021; 93(1):472–80. https://doi.org/10.1002/jmv.26260 PMID: 32621621

133. Yue H, Zhang M, Xing L, Wang K, Rao X, Liu H, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. Journal of Medical Virology. 2020; 92(1):2870–3. https://doi.org/10.1002/jmv.26163 PMID: 32530499

134. Yusuf E, Vonk A, van den Akker JPC, Bode L, Sips GJ, Rijnders BJA, et al. Frequency of Positive Aspergillus Tests in COVID-19 Patients in Comparison to Other Patients with Pulmonary Infections Admitted to the ICU. Journal of Clinical Microbiology. 2020.

135. Zhang C, Gu J, Chen Q, Deng N, Li J, Huang L, et al. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: A multicenter case series. PLoS Medicine. 2020; 17(6): e1003130. https://doi.org/10.1371/journal.pmed.1003130 PMID: 32544155

136. Zhang H, Zhang Y, Wu J, Li Y, Zhou X, Li X, et al. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerg Microbes Infect. 2020; 9(1):1958–64. https://doi.org/10.1080/22221751.2020.1812437 PMID: 32815458

137. Joseph C, Togawa Y, Shindo N. Bacterial and viral infections associated with influenza. Influenza Other Respir Viruses. 2013; 7 Suppl 2:105–13. https://doi.org/10.1111/irv.12089 PMID: 24034494

138. Klein EY, Monteforte B, Gupta A, Jiang W, May L, Hsieh YH, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respir Viruses. 2016; 10 (5):394–403. https://doi.org/10.1016/j.inod.2015.09.007 PMID: 27232677

139. Wongsurakiat P, Tulatamakit S. Clinical pulmonary infection score and a spot serum procalcitonin level to guide discontinuation of antibiotics in ventilator-associated pneumonia: a study in a single
institution with high prevalence of nonfermentative gram-negative bacilli infection. Therapeutic Advances in Respiratory Disease. 2018; 12:175346618760134.

140. Rawson TM, Wilson RC, Holmes A. Understanding the role of bacterial and fungal infection in COVID-19. Clin Microbiol Infect. 2021; 27(1):9–11. https://doi.org/10.1016/j.cmi.2020.09.025 PMID: 32979569

141. Garcia-Vidal C, Sanjuan G, Moreno-Garcia E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clinical Microbiology and Infection. 2021; 27(1):83–8. https://doi.org/10.1016/j.cmi.2020.07.041 PMID: 32745596

142. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, et al. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Glob Adv Health Med. 2013; 2(5):38–43. https://doi.org/10.7453/gahmj.2013.008 PMID: 24416692