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Frequency of coinfection by respiratory pathogens and its impact on the prognosis of patients with COVID-19

Dante M. Quiñones-Laveriano
Instituto de Investigación en Ciencias Biomédicas, Universidad Ricardo Palma. Lima, Perú,
dante.quinones@urp.edu.pe

Alonso Soto

Lucero Quilca-Barrera

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FREQUENCY OF COINFECTION BY RESPIRATORY PATHOGENS AND ITS IMPACT ON THE PROGNOSIS OF PATIENTS WITH COVID-19

FRECUENCIA DE COINFECCIÓN POR PATÓGENOS RESPIRATORIOS Y SU IMPACTO EN EL PRONÓSTICO DE PACIENTES CON COVID-19

Dante M. Quiñones-Laveriano[1], Alonso Soto[1,2], Lucero Quilca-Barrera[1], Italo Valero[1], Jhony A. de la Cruz-Vargas[1]

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ABSTRACT

Introduction: Co-infection between other microorganisms and SARS-CoV-2, such as viruses, bacteria and fungi, is an important factor in the management of COVID-19, which could increase the difficulties in diagnosis, management, prognosis, and even increase the mortality. **Objectives:** The objective of this review is to describe the published scientific evidence regarding coinfection in patients with COVID-19. **Methods:** A bibliographic search of studies published in Spanish or English was carried out using the PubMed, The Cochrane Library and Google Scholar search engines. Studies published between January 2020 and January 24, 2021 were assessed. **Results:** 25 articles from various continents (America, Asia and Europe) were included. All the studies had patients with a confirmed diagnosis of COVID-19 added to some other test that identified some co-infection. We identified 18 studies that showed bacterial coinfection, 17 studies of viral coinfection and 5 studies of fungal coinfection. The prevalence of coinfection showed extremely dissimilar figures according to the population studied and diagnostic criteria. **Conclusions:** The presence of coinfection seems to be linked to a higher frequency of unfavorable outcomes. However, it is important to develop Latin American studies, given the heterogeneity in the studies seen in different countries. Standardized definitions should be developed in order to be able to assess the impact of co-infections in patients with a diagnosis of COVID-19.

Key words: Co-infection; COVID-19; Review; Prognosis (source: MeSH NLM).

RESUMEN

Introducción: La coinfección entre otros microorganismos y el SARS-CoV-2, como virus, bacterias y hongos, es un factor importante en el manejo del COVID-19, el cual podría aumentar las dificultades en el diagnóstico, manejo, pronóstico, e incluso aumentar los síntomas y la mortalidad. **Objetivos:** El objetivo de la presente revisión es describir la evidencia científica publicada respecto a coinfección en pacientes con COVID-19. **Métodos:** Se llevó a cabo una búsqueda bibliográfica de estudios publicados en idioma español o inglés usando los buscadores de PubMed, The Cochrane Library y Google Scholar, se buscaron estudios publicados entre enero del 2020 hasta el 24 de enero del 2021. **Resultados:** Se incluyeron 25 artículos procedentes de diversos continentes (América, Asia y Europa). Todos los estudios contaron con pacientes con diagnóstico confirmado de COVID-19 sumado a alguna otra prueba que identifico alguna coinfección. Se identificaron estudios 18 estudios que mostraron coinfección bacteria, 17 estudios de coinfección viral y 5 estudios de coinfección fúngica. La prevalencia de coinfección mostro cifras extremadamente disimiles de acuerdo con la población estudiada y criterios diagnósticos. **Conclusión:** La presencia de coinfección parece ligarse a una mayor frecuencia de desenlaces desfavorables. Sin embargo, es importante desarrollar estudios latinoamericanos, dada la heterogeneidad en los estudios vista en los distintos países. Se deben desarrollar definiciones estandarizadas a fin de poder valorar el impacto de las coinfecciones en pacientes con diagnóstico de COVID-19.

Palabras clave: Coinfección; COVID-19; Revisión; Pronóstico (fuente: DeCS BIREME).

[1] Instituto de Investigación en Ciencias Biomédicas, Universidad Ricardo Palma, Lima-Perú.
[2] Departamento de Medicina Interna, Hospital Nacional Hipólito Unanue, Lima-Perú.

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INTRODUCTION

COVID-19, caused by the new coronavirus (SARS-CoV-2), in just four months since the first cases reported in the city Wuhan, the epicenter in China, could manage to infect millions of people around the world[1]. This new pandemic is characterized by rapid human-to-human transmission capacity and varied mortality due to acute respiratory distress syndrome (ARDS), multiple organ failure, and other serious complications[2].

Thanks to its rapid transmission capacity, infection and mortality rates (even when its lethality is relatively low) have come to exceed that of any other respiratory virus in this century. Various drugs are still in different clinical phases, so there is no specific management[3]. Despite the fact that most patients have a favorable prognosis, older and/or with underlying chronic conditions such as overweight, obesity, diabetes, hypertension, coronary heart disease, etc., they tend to have a poor evolution and a worse prognosis[4].

Co-infection between other microorganisms and SARS-CoV-2, such as viruses, bacteria, and fungi, could be an important factor in COVID-19, increasing difficulties in diagnosis, management, prognosis, and even increasing symptoms mortality[5]. Some studies suggest that coinfection with enterovirus (EV), rhinovirus (RV), metapneumovirus (MPV), and respiratory syncytial virus (RSV) could be common[5]. Likewise, it has been shown that coinfection by bacteria such as S. pneumoniae and S. aureus plays an important role in mortality and complications in cases of other viral pathogens, so it is recommended, in high-risk patients, the use of empirical antibiotic therapy in the face of poor clinical evolution[6].

Studies regarding the role of these coinfections in patients with COVID-19 remain scarce in Peru and in general in Latin American countries. Despite the scant evidence in this regard. Administration of antibiotics either as self-medication or in the context of hospital administration appears to be the rule. This review aims to describe the published scientific evidence regarding coinfection and its relevance in patients with COVID-19.

METHODS

PECO question formulation

The clinical questions addressed for this review were: What is the frequency of coinfection with respiratory pathogens in patients with COVID-19? Y Is coinfection with another respiratory pathogen a risk factor in people diagnosed with COVID-19?

- (P) oblation: Patient with a diagnosis of COVID-19
- (E) exposure: Having presented coinfection by another respiratory pathogen
- (C) control: Not having presented coinfection by another respiratory pathogen
- (O) outcome/outcome: Mortality, admission to the Unit Intensive Care Unit (ICU) or any other clinically relevant outcome.

Eligibility criteria

Studies that met the following were included:

- Being of type observational or clinical trials, which present data on the prevalence of coinfection and the association with its possible outcomes.
- Studies in patients with a confirmed diagnosis of COVID-19 by serological or molecular tests.

Studies that complied with: were excluded.

- Articles that did not present unpublished results, such as editorials, opinion articles, review articles, or systematic reviews.
- Studies in vitro or in animal models.
- Studies based on statistical simulation.
- Preprints or publications that have not passed a peer-review process.

Relevant systematic reviews were commented on in the discussion section.

Search strategy

A bibliographic search of studies published in Spanish or English was carried out using the PubMed, The Cochrane Library and Google Scholar search engines. We only searched for studies published in the course of 2020 and 2021 up to the date of January 24. The terms used for the search strategy are shown below:

("coinfection" OR "coinfected" OR "coinfecting" OR "coinfections" OR "coinfects") AND ("2019 nCoV" OR 2019nCoV OR"2019 novel coronavirus"OR" COVID 19 "OR" COVID-19 "OR" COVID19 "OR" new coronavirus "OR" novel coronavirus "OR" SARS CoV-2 "OR (Wuhan AND coronavirus) OR" SARS-CoV "OR" 2019-nCoV "OR" SARS-CoV-2 "OR" respiratory virus ").

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This search strategy was adapted to perform the search in each previously mentioned search engine.

Selection of evidence and data extraction

The selection of studies was carried out through a first stage consisting of identifying potentially relevant studies to answer the research question posed from the titles and summaries of the results thrown by the search engines. When applying the search strategy, this procedure was carried out by a single investigator. Subsequently, we proceeded to a second stage of reading the full text of each antecedent that has been identified as potentially relevant, at this point the selection criteria were evaluated and, if met, the article was selected to be part of the review, a single researcher carried out this process.

RESULTS

A total of 470 articles were found in the bibliographic search. After the selection and elimination of duplicate articles, and their reading, 62 studies were preselected for full-text reading. This procedure is summarized in Figure 1. Finally, 25 studies were included that met the inclusion criteria defined for conducting this research. (Look at Annex 1).

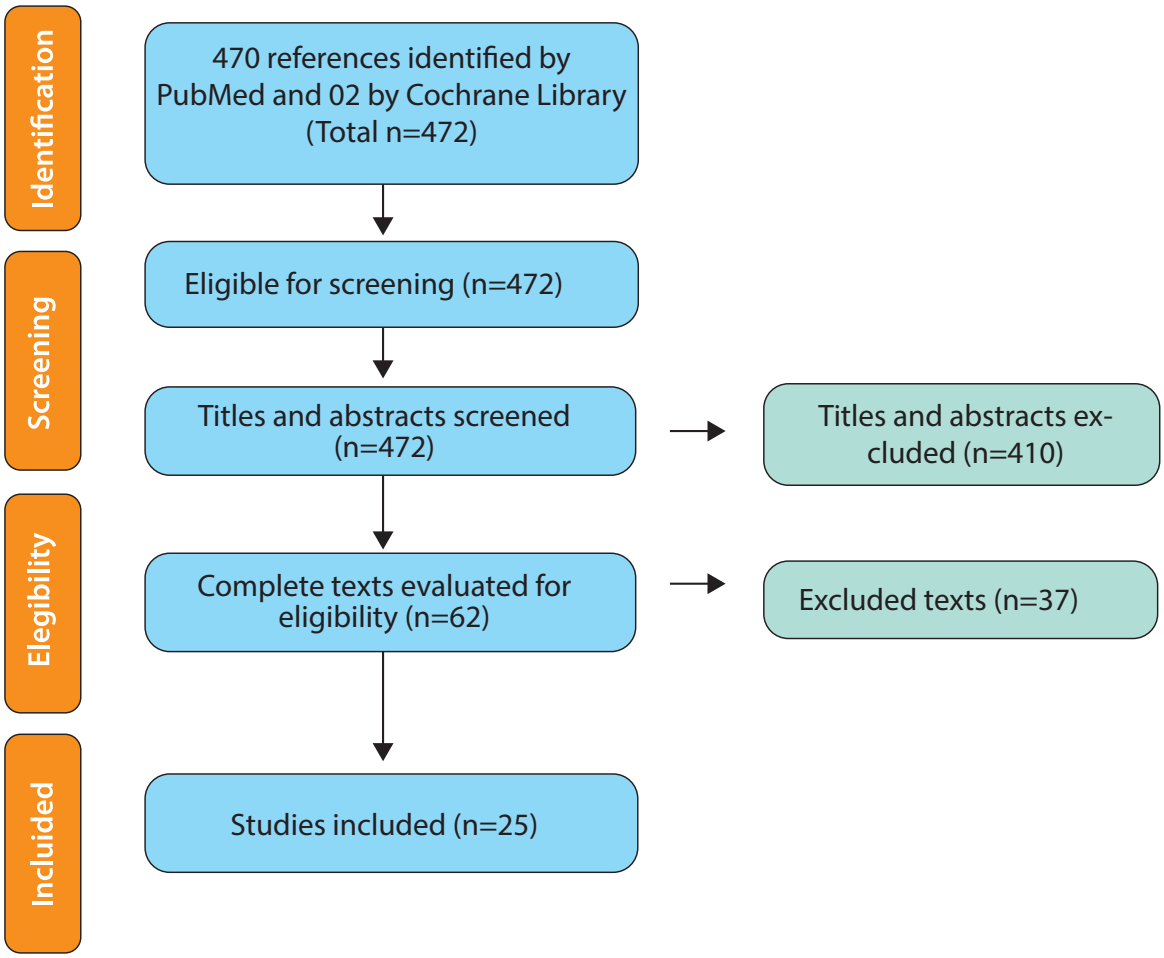

Figure 1. Study selection flowchart for review.

Table 1. Prevalence of bacterial coinfection in patients with COVID-19, review of studies.

Author (s)	Study location	Sample size	Diagnostic method	Prevalence of bacterial coinfection
He F. et al[28]	China	194	PCR	**Coinfección:** Streptococcus pneumoniae: 7,2% Bordetella pertussis: 10,3% Streptococcus pyogenes: 1,5% Staphylococcus aureus: 0,15% Neisseria meningitidis: 3,6% Haemophilus influenza: 8,8% Pseudomona aureginosa: 29,4% Global bacteriana: 50%
Garcia-Vidal, C et al[8]	Spain	989	Cultivo de muestras respiratorias	**Coinfection:** Streptococcus pneumoniae: 1,1% Staphylococcus aureus: 0,61% Haemophilus influenzae: 0,2% Moraxella catarrhalis: 0,1% General: 2,5% **Superinfection (associated with mechanical ventilation):** S. aureus: 0,4% P. aeruginosa: 0,3% Stenotrophomonas maltophilia: 0,2% K. pneumoniae: 0,1% **Superinfection (in-hospital pneumonia):** S. aureus: 0,1% P. aeruginosa: 0,1% Stenotrophomonas maltophilia: 0.1% K. pneumoniae: 0.1%
Hughes, S et al[9]	United Kingdom	836	Culture of respiratory samples	Coinfección: Staphylococcus aureus: 0,72% Pseudomonas spp: 1,44% Enterobacter spp: 0,6% Klebsiella spp: 0,7% Serratia spp:0,24%
Wu, Q et al[17]	China	74 pediatric patients	Nucleic acid test	Coinfección: Mycoplasma pneumoniae: 14,86%
Hazra, A et al[23]	United States	459	BioFire FilmArray 2 Respiratory Panel	Mycoplasma pneumoniae: 0% Chlamydophila pneumoniae: 0% Bordetella pertussis: 0%
Zhang, H et al[15]	China	38	Culture or metagenomic sequencing confirmed by RT-PCR	Secondary infection: K. pneumoniae: 28.95% Enterococcus faecium: 23.68% Acinetobacter baumannii: 21.1%

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Lehmann, CJ et al[25]	States United	321	Culture 21% Respiratory pathogens panel	Coinfection: Any: 2.2% Staphylococcus aureus: 0.6% Proteus mirabilis: 0.3% Coinfection: Bordetella parapertussis: 0.3%
Kim, D et al[19]	United States	116	Respiratory pathogens panel	Coinfection: Chlamydia pneumoniae: 0% Mycoplasma pneumoniae: 0%
Lv, Z et al[10]	China	354	Hemoculture Culture of alveolar bronchus lavage	Coinfección: Acinetobacter baumannii: 12,5 % E. coli: 12,5 % Staphylococcus haemolyticus: 5% P. aeruginosa: 5% Mycoplasma pneumoniae: 2,5% Stenotrophomonas maltophilia: 2,5% Enterococcus faecium: 2,5%
Zhu, X et al[20]	China	257	RT-PCR	Coinfection: 91,80%
Sharov, Konstantin S[11]	Russia	1204	Culture and subsequent biochemical or serological test	Superinfection: 35,96%
Zhou, F et al[7]	China	191	Culture	Secondary infection: 15%
Huang, C et al[24]	China	41	Culture	Secondary infection: 10%
Hirotsu, Y et al[12]	Japan	40	FilmArray respiratory panel	0%
Verroken A et al[16]	Belgium	32 (UCI)	FilmArray Respiratory Panel	Coninfection: 40,60%
Nieuwenhuis MB et al[29]	Netherlands	48 (UCI)	PCR	Superinfection: Staphylococcus aureus: 10.4% P. aureginosa: 2.1%
Intra J et al[30]	Italy	61 (UCI)	Ionization-Time of Flight Mass Spectrometry System with Matrix Assisted Laser Desorption	Lung colonization: P. aureginosa: 9,8% Staphylococcus aureus: 3,3% K. pneumoniae: 1,6% Escherichia coli: 1,6% Klebsiella oxytoca: 1,6% Enterobacter cloacae: 1,6% Staphylococcus epidermidis: 1,6%
Nori P et al[21]	United States	152 (99 de ellos en UCI)	Respiratory sample	Coinfection: Staphylococcus aureus: 44% P. aureginosa: 16% Klebsiella spp: 10% Enterobacter spp: 8% E. coli: 4% General: 46%

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Table 2. Prevalence of viral coinfection in patients with COVID-19, review of studies.

Author (s)	Place of study	Sample size	Diagnostic method	Prevalence of viral coinfection
Garcia-Vidal, C et al[8]	Spain	989	CRP	Coinfection: Influenza A: 0, 4% Influenza B: 0.2% Respiratory syncytial virus: 0.1%
Wu, Q et al[17]	China	74	Nucleic acid test	Secondary infection: Respiratory syncytial virus: 2.7% Ebstein Barr virus: 2.7 % Cytomegalovirus: 2.7% Influenza A: 1.35% Influenza B: 1.35%
Hazra, A et al[23]	United States	459	BioFire FilmArray 2 Respiratory Panel Coinfection	Coinfection: Adenovirus: 0.4% Coronavirus NL63: 0, 2% Huma n metapneumovirus: 0.4% Influenza A: 0.7% Parainfluenza 2: 0.2% Rest 0%
Zhang, H et al[15]	China	38	positive mNGS confirmed by RT-PCR	Coinfection: 15,79%
Lehmann, CJ et al[25]	United States	321	FilmArray respiratory panel Coinfection	Coinfection: Influenza A: 0.9% Rhinovirus / enterovirus: 0.6%
Kim, D et al[19]	United States	116	Respiratory pathogens panel	Coinfection: Influenza A: 0, 9% Influenza B: 0% Respiratory syncytial virus: 5.2% Parainfluenza 1: 0.9% Parainfluenza 2: 0% Parainfluenza 3: 0.9% Parainfluenza 4: 0.9% Metapneumovirus: 1.7% Rhinovirus / enterovirus: 6.9% Adenovirus: 0% Other coronaviruses: 4.3%
Lv, Z et al[10]	China	354	Kit for the detection of pathogenic nucleic acids	Coinfection: Mouth virus: 1.26% (of those evaluated)
Zhu, X et al[20]	China	257	RT-PCR	Coinfection: 31,50%

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Sharov, KS[11]	Russia	1204	Culture and subsequent biochemical or serological test	Coinfection: 26,08%
Hirotsu, Y et al[12]	Japan	40	FilmArray respiratory panel	Coinfection: Rhinovirus / Enterovirus: 27.5% Metapneumo virus: 17.5% Coronavirus 229E: 10% Coronavirus OC43: 7.5% Adenovirus: 5% Respiratory syncytial virus: 5% Coronavirus NL63: 2.5% Adenovirus: 2.5%
Ma, S et al[13]	China	93	indirect immunofluorescence IgM	Coinfection: Virus Influeza a: 47.3% influenza virus B: 2.2%
Yue, H et al[18]	China	307	IgM Serology	Coinfection: influenza a: 49.8% influenza B : 7.5%
Nowak, MD et al[14]	United States	1204	Respiratory Panel PCR2, Flu / RSV PCR	Coinfection: Influenza A: 0.08% Influenza B: 0% Respiratory syncytial virus: 0.31% Coronavirus NL63: 0 , 63% HKU1 Coronavirus: 0.45% 229E Coronavirus: 0.36% OC43 Coronavirus: 0.09% Rhinovirus / Enterovirus: 0.73% Metapneumovirus: 0.36% Adenovirus: 0.18% Parainfluenza: 0%
Leuzinger, K et al[27]	Switzerland	930	Multiple respiratory viral panel	Coinfection: Human coronavirus: 0.54% Rhinovirus: 0.54% Parainfluenza virus: 0.32% Influenza A: 0.22% Adenovirus: 0.11% Respiratory syncytial virus : 0.11%
Si, Y et al[22]	China	24	Multiple respiratory viral panel	Coinfection: 4,20%
Lin, D et al[31]	China	92	Multiplex 2.0 rapid detection kit	Coinfection: 3,20%
Wee, LE et al[26]	Singapore	431	Respiratory viral pathogens panel	Coinfection: 1,39% General

Table 3. Prevalence of fungal coinfection in patients with COVID-19, study review.

Author (s)	Study location	Sample size	Diagnostic method	Prevalence of fungal coinfection
Hughes, S et al[9]	United Kingdom	836	GeneXpert	Infección secundaria: Candida spp: 2,87% Aspergillus spp: 0,36%
Zhang, H et al[15]	China	38	RT-PCR	Coinfection: 5,26%
Lv, Z et al[10]	China	354	Alveolar bronchial lavage culture	Coinfection: Candida albicans: 7,% Candida tropicalis: 2.5% Candida parapsilosis: 2.5% Candida lusitaniae: 2.5%
Zhu, X et al[20]	China	257	RT-PCR	Coinfection: 23,30%
Intra J et al[30]	Italy	61 (UCI)	Alveolar bronchial lavage culture	Coinfection: Candida albicans: 23% Candida glabrata: 6.6% Aspergillus fu migatus: 1.6%

Table 4. Main outcomes in the presence of coinfection or superinfection in patients with COVID-19, review of studies.

Author (s)	Study place	Sample size	Outcomes
Garcia-Vidal, C et al[8]	Spain	989	Coinfection by a bacterial, viral or fungal pathogen increased ICU admission by almost double (25.8% vs 11.9%; p = 0.02), but there was no statistically significant relationship with mortality (16.1% vs 9.4%; p = 0.21). Superinfection by a bacterial, viral or fungal pathogen increased admission to the ICU (67.4% vs 11.9%; p <0.001) and mortality (18.6% vs 9.4%; p = 0.047).
Hughes, S et al[9]	United Kingdom	836	Having coinfection detected by blood culture was associated with a RR of mortality of 1.51 (p = 0.3543), while having coinfection detected by sputum culture had a RR of 0.90 (p = 0.8462).
Zhang, H et al[15]	China	38	Patients with secondary infection had: a lower rate of hospital discharge in a 60-day follow-up (log rank p <0.001), greater need for mechanical ventilation (86.36% vs 25% ; p <0.0001) and higher mortality (36.4% vs ~ 7%).

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Lv, Z et al[10]	China	354	Coinfection with other respiratory pathogens (bacterial or fungal), as well as lymphocytes and D-dimer were associated with severity of COVID-19 (R = 0.375 p <0.001).
Sharov, Konstantin S[11]	Russia	1204	Mortality in patients without coinfection was 1.3%, in patients with viral coinfection 4.2%, in patients with bacterial superinfection 18.2% and in patients with viral and bacterial coinfection 15 ,1%.
Ma, S et al[13]	China	93	Mortality among patients coinfected with influenza was 47.82% and among non-coinfected patients it was 46.81%, without statistically significant association.
Wee, LE et al[26]	Singapore	431	Mortality in coinfected was 0% (0/6), while in non-coinfected it was 0.23% (1/425), with no statistically significant association.

Study characteristics:

The articles we chose were developed on various continents such as America (United States), Europe (Spain, Russia, Switzerland, Netherlands, Italy, United Kingdom, and Belgium), and Asia (China, Japan, Singapore). Most of the studies were longitudinal, with 9 retrospective cohorts[7–15], 1 prospective cohort[16]; While of the cross-sectional studies, 8 studies were analytical[17–24], and 4 studies were cross-sectional descriptive[25–28]. 3 letters to the scientists[29–31] were included. Most of these studies were conducted in a hospital setting (including both outpatients and inpatients); however, some also included patients admitted to the ICU[16,21,29,30]. The increased risk of mortality and severity of the disease were also identified in some studies[8–11,26]. The number of patients had a wide variability (from 24 to 8488).

Findings:

Bacterial

coinfection The risk of bacterial coinfection ranged between 0%[12,19,23] and 91.8%[20] according to the definitions used, the type of patients included, and the diagnostic methods used. The studies carried out based on molecular biological techniques reported frequencies between 0%[12,19,23] and 91.8%[20], while the results based on conventional cultures showed a frequency between 1.2%[32] and 46%[21]. In general, the bacteria most frequently found were S. aureus and P. aeruginosa, although the enormous variability prevents obtaining a summary measure.

Lv et al. found that the most frequently found bacteria were Acinetobacter baumannii and E. coli with 12.5% both[10]; Wu Q. et al. found a prevalence of coinfection of Mycoplasma pneumoniae 14.9%, in a study carried out in 74 pediatric patients[17]; on the other hand, He F. et al. found a prevalence of P. aeruginosa of 29.4% and of Bordetella pertussis of 10.3%[28]. In the United States, Lehmann CJ. et al. found a prevalence of bacterial coinfection of 2.2%; in which the most frequently found bacteria was S. aureus with 0.6%[25]; in this same country, Hazra A. et al.[23] and Kim D et al.[19] did not find bacterial coinfection in hospitalized patients; in the United States also, Nori P. et al. found a prevalence of bacterial coinfection of 59.8% in 152 patients from the Intensive Care Unit (ICU); where the most frequent bacteria were S. aureus with 44% and Pseudomona aureginosa with 16%[21]. In the United Kingdom, in a study carried out in 836 patients, a prevalence of coinfection by Pseudomona spp. 1.44%, S. aureus 0.72%, Klebsiella spp. 0.7%, Enterobacter spp. 0.6% and Serratia spp. 0.24%[9]. Also, in a study of 989 patients hospitalized for at least 48 hours in Spain, a prevalence of

bacterial coinfection of 3.1% was found, being mainly caused by Streptococcus pneumoniae with 1.21% and S. aureus with 0.61%[8]. A study based on a definition developed by a multidisciplinary team in 1016 patients in the United States of America found a rather low rate of coinfections, including 1.3% of cases of confirmed bacterial pneumonia and 1.1% of cases of bacterial pneumonia probable. Although 69% of patients received antibiotic therapy on admission, it was stopped in most patients within 48 hours of admission in the absence of demonstration of pathogens[32].

Another important aspect evaluated was superinfection, which consists of a bacterial infection added to the patient after the diagnosis of COVID-19. In Russia, a study in 1204 hospitalized patients found a prevalence of bacterial superinfection in patients of 35.96%[11]; On the other hand, in the Netherlands, 48 patients in the ICU had a superinfection by S. aureus of 10.4% and by Pseudomona aureginosa of 2.1%[29]. In China, two studies found prevalences of over infection of 10% and 15%[7.24]; while, in patients with severe and critical illness, a proportion of respiratory over infection of 55.3% was found, where 76.9% of the pathogens found were bacteria[30], the most frequent being K. pneumoniae with 28 , 95%; Enterococcus faecium with 23.68%; Acinetobacter baumannii with 21.1%. In Spain, superinfection in hospitalized patients was 4.7%, of these patients, the main bacteria associated with mechanical ventilation were S. aureus (0.4%), P. aeruginosa (0.3%), Stenotrophomonas maltophilia (0.2%) and K. pneumoniae (0.1%); while the most common bacteria in hospital pneumonia were: S. aureus (0.1%), P. aeruginosa (0.1%), Stenotrophomonas maltophilia (0.1%) and K. pneumoniae (0.1%)[8].

Viral coinfection

The risk of viral confection fluctuated between 0.08%[14] and 49.8%[18], the most frequent viruses being Influenza A, Influenza B, Respiratory syncytial virus and Rhinovirus/enterovirus.

Concerning viral co-infections, in a study in Russia, the prevalence of viral coinfection was 26.1%[11]. Studies in China find prevalences of viral coinfection ranging from 3.2% to 31.5%[20,22,31]; the virus most frequently found was influenza A, with 47.3% and 49.8% in two different samples of hospitalized patients, while the influenza B virus was found in 2.2% and 7.5%; in the respective samples[13,18]. In contrast, the viruses most frequently found in children were respiratory syncytial virus (2.7%), Ebstein Barr virus (2.7%), and cytomegalovirus (2.7%); above Influenza A and B viruses, with 1.35% each. On the other hand, studies carried out in the United States find prevalences of coinfection by influenza A virus lower than those reported in China, such as 0.08% (14), 0.7% (23) or 0.9% (19.25); while the influenza B virus was absent in the reviewed studies (14,19,23); other viruses such as rhinovirus / enterovirus were found to be co-infecting in 0.6% (25), 6.9% (19) and 0.73% (14); respiratory syncytial virus in 5.2% (19) and 0.31% (14); while other coronaviruses were found to co-infect COVID-19 patients in 4.3% (19) or less (14). Similar results were found in Spain, where viral coinfection was 0.4% for Influenza A, 0.2% for Influenza B, and 0.1% for a respiratory syncytial virus (8). On the other hand, in a study with 930 patients in Switzerland, coinfection by human coronavirus of 0.54%, rhinovirus of 0.54%, parainfluenza virus of 0.32%, influenza A of 0.22%, adenovirus of 0.11% and respiratory syncytial virus 0.11% (27). On the other hand, in a study of 40 patients in Japan, the viral coinfection for rhinovirus / enterovirus was 27.5%, metapneumovirus 17.5%, coronavirus 229E 10%, coronavirus OC43 7.5%, adenovirus 5%, virus respiratory syncytial virus 5%, coronavirus NL63 2.5% and adenovirus 2.5% (12). Virus superinfection was reported in fewer studies, with a frequency of 15.79% in a study conducted in 38 patients with severe or severe diseas[e(15)].

Fungal

Coinfection Fungal coinfection was reported with a frequency ranging from 0.36% (9) to 23.3% (20), with Candida spp and Aspergillus being the most frequently reported fungi.

Fungal coinfection was reported less frequently. Studies in China indicate that it remained between 5.26% (15) and 23.3% (20); Lv et al. found that, from the culture obtained from alveolar bronchial lavage in 354 patients, the prevalence of coinfection Candida albicans was 7.5%, Candida tropicalis was 2.5%, Candida parapsilosis was 2.5% and Candida lusitaniae was 2.5% (10). In Italy, in a study of 61 patients admitted to the ICU, it was found that the coinfection by Candida albicans was 23%, by Candida glabrata it was 6.6% and by Aspergillus fumigatus it was 1.6% (30). While, with regard to over-infection, in the United Kingdom, using the GGG diagnostic method in 836 patients, the prevalence for Candida spp was 2.87% and for Aspergillus spp it was 0.36% (9).

Risks associated with coinfection

García Vidal et al. indicated that coinfection increased ICU admission by almost double (p = 0.02), but there was no statistically significant relationship with mortality (p = 0.21). On the other hand, superinfection significantly increased ICU admission (p <0.001) and mortality (p = 0.047)[8]. In the same way, Hughes et al. mentions that those patients who had pathogens identified in their blood had a higher relative risk of death, but not statistically significant, compared to the initial value of hospitalized patients (P: 0.3543)[9].

On the other hand, Zhang, H et al.[15] indicated there was a lower rate of hospital discharge in patients with secondary infection in a follow-up of 60 days (log rank p <0.001), greater need for mechanical ventilation (86.36% vs 25%; p <0.0001) and higher mortality (36.4% vs around 7%). Likewise, Lv Z et al.[10] indicates that when coinfected with bacterial or fungal pathogens, lymphocyte and D-dimer values associated with the severity of COVID-19 were obtained (R = 0.375 p <0.001).

Regarding mortality, Sharov KS[11] points out that in patients without coinfection it was 1.3%, in patients with viral coinfection 4.2%, in patients with bacterial superinfection 18.2%, and in patients with viral and bacterial coinfection 15 ,1%. In contrast to studies by Ma, S et al.[13] and Wee LE et al.[26] where they indicate that there was no statistically significant association in relation to mortality with coinfected or non-coinfected patients.

Coinfection in critically ill patients

Four studies evaluated bacterial coinfection in critically ill patients[16,21,29,30], with being the common microorganism among the four studies Staphyloccoco Aureus, and were also identified Pseudomonas auroginosa and Klebsiella pneumoniae as the cause of coinfection, superinfection, and bacterial colonization. A study was identified in relation to fungal coinfection in critically ill patients; this study by Intra J et al, mentions that pathogenic fungi such as Candida albicans (23%), Candida glabrata (6.6%) and Aspergillus fumigatus (1.6%)[30]. According to Lv Z et al., critically ill patients had the highest mortality, lowest lymphocyte count, highest D-dimer levels, and the highest rate of coinfection with bacteria/fungi[10].

DISCUSION

The presence of coinfection was extremely variable according to the type of patient, the diagnostic method used, and the country of study. The results of previous systematic reviews and meta-analyzes show heterogeneous results. Studies conducted in China found high prevalence of bacterial coinfection, from 50% in a study of 194 patients[28] to 91.8% in 257 hospitalized patients[20].

Lansbury et al.[1], in a meta-analysis with a joint population of 3834 patients, found a prevalence of bacterial coinfection of 7%; Likewise, another meta-analysis with a joint population of 3338 found that bacterial coinfection was 3.5% (33) For viral coinfections, systematic reviews find prevalences of 3% (1) and 8.45% (34); being 1.49% the frequency of coinfection by Influenza A and 0.42% by Influenza B[35].

The absence of standardized criteria to define the presence of coinfections does not allow us to estimate the problem of coinfection worldwide. The enormous heterogeneity of the results does not allow for synthesis measures (meta-analysis). Likewise, the frequency of coinfection depends to a great extent on the country where the study is carried out. The results cannot be extrapolated between the different countries. No studies were identified in Latin America, so it is necessary to have more information at the regional level.

Most studies do not differentiate colonization from coinfection. This is particularly important for molecular biology studies that show reports of coinfection with much higher prevalences than studies based on bacterial cultures. On the other hand, conventional bacterial cultures are generally not very sensitive for detecting respiratory pathogens[36,37].

Many of the more recent studies and particularly those that have developed standardized definitions of coinfection (explicitly differentiating it from colonization), show that coinfections appear to be relatively rare. However, since the variability between countries means that the results shown cannot be extrapolated to Peru, it is important to generate local evidence to support decision-making. This is particularly important in Peru, where the irrational use of antibiotics against COVID has alarming levels[38,39].

In many studies, the presence of coinfection was associated with the presence of unfavorable outcomes. This could be relevant, particularly in patients with more aggressive evolution patterns. However, the evidence in this regard is not conclusive yet. Studies are needed to evaluate this possible association. Suppose coinfection plays an important role in mortality or complications. In that case, improvement in methods based on conventional cultures and the implementation of molecular diagnosis should be considered in most hospitals that care for the most critical patients.

Within the limitations of the present review, it is found that many studies did not make a clear difference about the report of coinfection and colonization, so these proportions could have been overestimated. On the other hand, since the risk of coinfection depends a lot on geographical location and the characteristics of the population, the absence of studies in our region is also a limitation, since a reality similar to that found in Peru, where the empirical use of antibiotics is not exactly uncommon.

CONCLUSION

The review includes 25 articles from various continents (America, Asia, and Europe). All the studies had patients with a confirmed diagnosis of COVID-19 added to some other test that identified some co-infection. We note that the studies have very heterogeneous populations in quantity and clinical and epidemiological profiles.

Eighteen articles were identified that showed bacterial coinfection. The risk of bacterial coinfection reached 91.8% with molecular methods and 46% with conventional culture. The most frequently encountered bacteria were S. aureus and P. aeruginosa.

17 articles were identified concerning viral coinfection, where the risk of viral confection reached 49.8%, the most frequent agents being Influenza A, Influenza B, respiratory syncytial virus and rhinovirus / enterovirus.

Five articles reported fungal coinfection in critically ill patients, which reached 23.3%, the most frequent fungal agents being Candida spp and Aspergillius spp.

The findings showed a greater frequency of suffering from severe disease and mortality in the presence of coinfection. However, the heterogeneity of the results implies the need for more specific studies.

REVIEW ARTICLE

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Correspondence: *Dante M. Quiñones-Laveriano*
Address: *Jirón Junín #881 Dep. C-103. Lima, Perú.*
Telephone: *984725252*
Email: *dante.quinones@urp.edu.pe*

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