REVIEW ARTICLE

https://doi.org/10.26432/1809-3019.2022.67.020

Association of COVID-19 to multidrug-resistant bacterial superinfections and coinfections: an integrative review

Associação da COVID-19 às superinfecções e coinfecções bacterianas multirresistentes: revisão integrativa

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ABSTRACT

Introduction: COVID-19 is a pandemic disease that may be related to concomitant or secondary events to its manifestation, such as bacterial coinfections and superinfections. Another relevant aspect of this hypothesis is the participation of multidrug-resistant agents in health care and the conscious use of antibacterial agents. **Objective:** The aim of this study was to describe the bacteria that participated in multidrug-resistant bacterial coinfections and superinfections associated with COVID-19 in hospitalized patients according to the scientific literature from March 2020 to June 2021. **Method:** Integrative review (IR) of the literature, this descriptive study was structured according to its six characteristic phases. To this end, the Regional Portal of the Virtual Health Library (VHL) and PubMed were our search bases. **Results:** This IR obtained studies from different methods and countries that highlighted an important participation of male patients with COVID-19, as well as the use of immunosuppressants, immunomodulators, and antibiotics prior to multidrug-resistant bacterial infections. The Gram-negative bacteria were evident in coinfection and superinfection, standing out for their resistance profile, especially the classes of beta-lactams, quinolones, macrolides, and sulfonamides, as well as the producers of extended-spectrum beta-lactamases (ESBL), metallo-beta-lactamases (MBL), and carbapenemases enzymes. In the Gram-positive bacteria present, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE) stood out with resistance to the other analyzed classes. **Conclusion:** The Gram-negative bacteria were more present in episodes of coinfection and superinfection multidrug-resistant in COVID-19, whose resistance profile encompassed the classes of beta-lactams, quinolones, macrolides, and sulfonamides, as well as the producers of ESBL, MBL, and carbapenemases enzymes. MRSA and VRE were prominent among the identified Gram-positive bacteria, and they were resistant to other classes analyzed in the sample.

Keywords: COVID-19, Superinfection, Coinfection, Bacteria, Antibacterial agents.

RESUMO

Introdução: A COVID-19 é uma doença pandêmica que pode estar relacionada a eventos concomitantes ou secundários à sua manifestação, como as coinfecções e superinfecções bacterianas. Outro aspecto relevante nessa hipótese é a participação de agentes multirresistentes no cuidado em saúde e no uso consciente dos antibacterianos. **Objetivo:** Descrever os agentes participantes nas coinfecções e (ou) superinfecções bacterianas multirresistentes associadas à COVID-19 em pacientes hospitalizados conforme a literatura científica de março de 2020 a junho de 2021. **Método:** Revisão integrativa (RI) da literatura, descritiva e estruturada conforme as suas seis fases características. Para tal, o Portal Regional da Biblioteca Virtual em Saúde (BVS) e a PubMed foram nossas bases de busca. **Resultados:** Esta RI obteve estudos de diferentes métodos e países que realçaram uma importante participação de pacientes do sexo masculino com COVID-19, bem como o uso de imunossupressores, imunomoduladores e antibióticos previamente as infecções bacterianas multirresistentes. As bactérias Gram-negativas foram evidentes tanto na coinfecção quanto na superinfecção, se destacando pelo seu perfil de resistência principalmente as classes dos beta-lactâmicos, quinolonas, macrolídeos e sulfonamidas; e produtoras das enzimas beta-lactamases de espectro estendido (ESBL), Metalo-beta-lactamases (MBL) e carbapenemases. Nas Gram-positivas presentes se destacaram *Staphylococcus aureus* meticilina resistentes (MRSA) e *Enterococcus faecalis* resistentes à vancomicina (VRE) com resistência às outras classes analisadas. **Conclusão:** As bactérias Gram-negativas foram mais presentes nos episódios de coinfecção e superinfecção multirresistentes associadas à COVID-19, cujo perfil de resistência abrangeu as classes dos beta-lactâmicos, quinolonas, macrolídeos e sulfonamidas, bem como a produção das enzimas ESBL, MBL e carbapenemase. MRSA e VRE são destaques entre as Gram-positivas identificadas, sendo estas resistentes às outras classes colocadas em análise na amostra.

Palavras-chave: COVID-19, Superinfecção, Coinfecção, Bactérias, Antibacterianos.

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Article received: 12/04/2021. Article approved: 09/15/2022. Article published: 11/23/2022.
Responsible Editor: Prof. Dr. Eitan Naaman Berezin (Editor-in-Chief).

INTRODUCTION

SARS-CoV-2 is a zoonotic RNA virus that first manifested itself in the last weeks of 2019 in Wuhan, China, which is responsible for causing a still-pandemic clinical condition known as COVID-19. This is a microorganism of the Coronaviridae family, whose origin hypothesis considered bats and the Malayan pangolin due to the genetic proximity between the CoVs found in these animals and the current one. When interacting with human cells, SARS-CoV-2 demonstrated an affinity for angiotensin-converting enzyme 2 (ACE2) receptors, and it uses one of the proteins, such as spike glycoprotein or viral S protein, so that coronaviruses are able to decode in order to move away from the action of antibodies, and undergo cleavage caused by type II transmembrane serine protease (TMPRSS2), proceeding with viral activation, virus-cell membrane fusion, and cell invasion. Its entry into the cell can also occur through virus-endosome fusion with the aid of cleavage by the cathepsin-L enzyme(1-3).

The importance of adherence to contact and respiratory precautions is highlighted due to their effectiveness in preventing SARS-CoV-2 infection. Also, noteworthy is the immunization of the entire population without restrictions associated with its application as the only protective measure against COVID-19. This disease tends to cause more severe signs and symptoms in populations with certain characteristics and/or previous chronic degenerative conditions, such as individuals aged 60 years or older with cardiovascular disease and diabetes *mellitus*(2-4).

Although there is still no specific and effective treatment for COVID-19, other measures are used in practice to compensate for the most evident pathophysiological changes in severe cases, such as oxygen therapy, antibiotic therapy if there is a suspicion or confirmation of bacterial infection, volume replacement, and relief of symptoms in order to intervene in the chances of mortality. During the pandemic, different controversies arose in relation to early medicalization or used in severe cases of the disease, barring them due to contraindication or scientific insufficiency; corticosteroids, vitamin D analogs, anthelmintics, antivirals, and antibiotics are special classes related to this point(3,5).

A systematic review of the literature showed that there are uncertainties regarding the "benefits or risks of using antibiotic therapy in patients with COVID-19 without evidence of bacterial infection"(6). In addition, a guideline published in June 2020(7) indicated that antibacterial agents can be used in patients with COVID-19 only if there is evidence or suspicion of bacterial infection. Therefore, its prophylactic use in patients with COVID-19 did not show consistent bases and it could be a risk for the manifestation of adverse events, antimicrobial resistance, and increases in hospital expenses.

In addition, more concerns are added to patients hospitalized due to COVID-19, which correspond to Healthcare-Associated Infections/Hospital Infections (HAIs/IH), coinfections, or superinfections. Bacteria, fungi, viruses, and protozoa have been documented as causing these events(8-13).

HAIs/IH are infectious processes resulting from individual stay in the hospital environment and also encompass some situations detected after discharge. In general, its incidence is autonomous in relation to the environment, that is, more dependent on the endogenous than the exogenous environment. They are related to the patients and procedures that are part of health care; however, they can affect anyone who frequents the hospital. A nosocomial infection is an event detected from clinical and laboratory data, in which the time frame varies according to the unit the patient is in; in the intensive care unit (ICU), for example, the variation is up to 48 h after discharge(14).

When the infection is diagnosed or incubated at the time the patient is admitted to the hospital, considering the absence of a previous admission history, it is a community infection; if there is an aggravation of this process after admission, without evidence of the manifestation of another microorganism, it is still classified as such. Furthermore, it is considered a coinfection when two infectious agents act simultaneously(9,14).

In turn, superinfection is an event that is influenced by antibiotic drug therapy, resulting in an opportunistic colonization of a secondary pathogen in individuals immunosuppressed by primary pathogens(9,15). *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and vancomycin-resistant *Enterococcus faecalis* (VRE) are examples of health care-related opportunistic pathogens, in addition to being multidrug-resistant bacteria, that is, microorganisms not susceptible to at least one antibacterial in three or more classes of antibiotics(16).

Considering the relevance of multidrug-resistant bacteria in health care and in the conscious use of antibiotics, as well as the importance of highlighting the participation of these agents in the pandemic scenario, the objective of this study was to describe the bacteria that participated in multidrug-resistant bacterial coinfections and superinfections associated with COVID-19 in hospitalized patients according to the scientific literature from March 2020 to June 2021.

METHODS

This was an integrative review (IR) of the literature. Its methodological structure was composed of six vital phases(17), which shaped this IR.

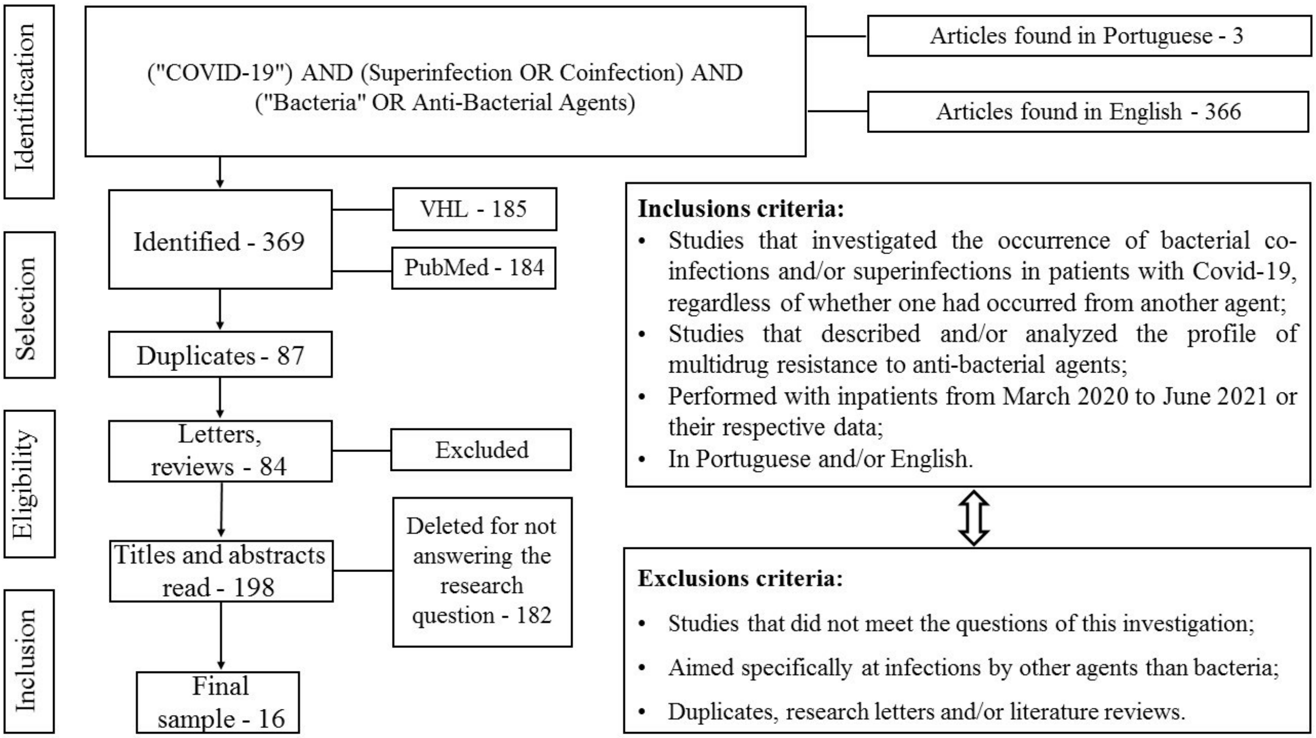
This study was only submitted to the evaluation of the Scientific Committee of the Nursing Course (SCNC) of the authors' faculty of origin, which approved it in protocol n° 013/21. Data collection took place after approval at the indicated location. Furthermore, Law 9.610/1988, which deals with the preservation of copyright, is the ethical reference for writing this study(18).

In the first phase, there are the following questions: Which multidrug-resistant bacteria participate in coinfections and/or superinfections associated with COVID-19 in hospitalized patients? What is the resistance profile in relation to them? The acronym PICO was not used for the construction of the research questions, but they were determined from the justification and objective of this study. The search was carried out in July 2021 in the following databases: Regional Portal of the Virtual Health Library (VHL) and PubMed. The Boolean operators "*AND*" and "*OR*" helped to combine the Health Sciences Descriptors (HSD) and Medical Subject Headings (MeSH), resulting in ("Covid-19") *AND* (Superinfection *OR* Coinfection) *AND* ("Bacteria" *OR* Anti-Bacterial Agents). Thus, the HSD and MeSH were applied in these two databases to obtain articles in Portuguese or English, published in 2020 or 2021. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(19) were used to organize this study.

The second methodological phase started earlier is concluded as of determination of the inclusion and exclusion. Therefore, the following studies were included: those that investigated the occurrence of bacterial coinfections and/or superinfections in patients with COVID-19, regardless of whether one had occurred from another agent; those that described and/or analyzed the profile of multidrug resistance to antibacterials; those that were performed with inpatients from March 2020 to June 2021 or their respective data; and those that were published in Portuguese and/or English. Studies that did not meet the questions of this investigation, as well as those that aimed specifically at infections by other agents than bacteria, duplicates, research letters, and/or literature reviews, were excluded.

In the third phase of the IR, we adapted an instrument adopted by Souza et al.(17) to assist in the registration of articles selected for the final sample, which was structured with the following elements: authorship, country, language, year of publication, research objective or question, assessment of methodological rigor, level of evidence, and results and analysis of the conclusion according to the objective of the study. Google Docs® and Google Sheets® applications were used for data storage and organization. A hierarchical evidence classification system(20) was used to classify the studies.

The fourth phase is corresponding to the critical analysis of articles included in this IR based on the inclusion and exclusion criteria. Titles and abstracts were read to select the articles in order to read in full, which resulted in the selection of 16 articles (Figure 1). Finally, the final sample



Source: Own elaboration, 2021.

Figure 1 – Flowchart with the steps of the integrative review. São Paulo, São Paulo, July 2021.

was determined and synthesized for knowledge purposes according to the instrument of the third phase. In the fifth phase, the results are described and discussed, and in the sixth phase, the IR is presented; both occur below. Figure 1 is a graphic element developed according to the example presented by Cruz et al.(21).

RESULTS

After applying the phases described earlier, a sample of 16 studies was obtained for its composition: 11 were identified in the VHL Regional Portal and the others in PubMed; 62.5% (10/16) corresponded to the year 2020; 50% (8/16) of the studies corresponded to level 3; 25% (4/16) corresponded to level 2; and 12.5% corresponded to levels 4 and 5, respectively. In addition, 50% of the studies were carried out in European countries, followed by 25% in North America, 6.25% in Africa, and the rest in Asia. All were published in English.

Eleven studies had more or only male patients(22-32); in two studies, the same situation occurred with female patients(33,34); and in three studies, these data were not identified(35-37). Diabetes *mellitus*, systemic arterial hypertension, chronic kidney disease, respiratory diseases, and cardiovascular diseases were common comorbidities in more than two studies(22,23,25-30,32-34).

Some drugs were used by populations studied before the multidrug-resistant bacterial infections were detected, as well as immunosuppressants such as mycophenolic acid and corticosteroids(22-27,29-31,34); immunomodulators such as leronlimab, sarilumab, tocilizumab, and tacrolimus(22-27,29-31,34); and antibiotics covering the class of broad-spectrum penicillins, cephalosporins, carbapenems, quinolones, glycopeptides, tetracyclines, and others(22-26,28,30-32,34).

In 62.5% of the sample, there were episodes of bacterial superinfections, while 25% analyzed only those of coinfection and 12.5% analyzed both types.

Regarding the multidrug-resistant bacteria participating in the coinfection episodes, it is noteworthy that the isolated Gram-negative bacteria were more resistant to the following antibiotics: amoxicillin, clavulanic acid, cefoxitin, erythromycin, clindamycin, piperacillin + tazobactam, ciprofloxacin, levofloxacin, sulfamethoxazole + trimethoprim, tigecycline, ceftazidime, cefotaxime, ceftriaxone, cefepime, meropenem, and imipenem. The species *P. aeruginosa*, *Enterobacter cloacae*, *Escherichia coli*, *K. pneumoniae*, and *A. baumannii* represent this profile; in addition, extended-spectrum beta-lactamases (ESBL), carbapenemases, and New Deli metallo-beta-lactamase (NDM) were the main modifying enzymes of the bacterial response to antibiotics related to them. The Gram-positive bacteria were represented by *S. aureus*, S. *epidermidis*, *Streptococcus pneumoniae*, and *E. faecalis*, whose resistance analysis covers mainly the antibiotics just mentioned earlier: methicillin to *S. aureus*; methicillin only to *S. epidermidis*; amoxicillin, clavulanic acid, cefoxitin, erythromycin, clindamycin, piperacillin + tazobactam, ciprofloxacin, levofloxacin, and sulfamethoxazole + trimethoprim to *Streptococcus pneumoniae*; and only amoxicillin, gentamicin, piperacillin + tazobactam, ceftriaxone, meropenem, and imipenem to *E. faecalis*. These bacteria have been isolated from the bloodstream, respiratory tract, urine, and rectal swab, causing bacteremia, bilateral pulmonary infiltrate, urinary tract infection, and a complication of the course of COVID-19(25,27,30,32-34).

In the episodes of superinfection, the Gram-negative bacteria were also predominant(22,24-26,28-31,35,36) and characterized as follows: Enterobacteria that produce ESBL, metallo-beta-lactamases (MBLs), and carbapenemases, represented by the species *K. pneumoniae*, *Klebsiella oxytoca*, and *E. coli*; and non-fermenting bacilli producing MBLs and resistant to aminoglycosides, beta-lactams, phenicol drugs, macrolides, quinolones, sulfonamides, and fosfomycin, with *Stenotrophomonas maltophilia*, *A. baumannii* in common in two of the studies, and *P. aeruginosa* in common in three of the studies. Furthermore, Gram-positive bacteria were portrayed with intersection by *S. aureus* (MRSA) in four of the texts(23,25,26,28) and VRE in three(25,31,37); in contrast, methicillin-resistant coagulase-negative *Staphylococci* (SCoN) were identified in only one of them(26).

Chart 1(22-37) highlights the main data by text according to relevance for this study.

DISCUSSION

This IR obtained more studies involving male patients with COVID-19, which is an additional independent risk factor in the most severe cases of this pathology, in addition to the main comorbidities highlighted and the use of immunosuppressive drugs that favor this outcome(3,38-40). Gram-negative bacteria were more evident in coinfection and superinfection, standing out for their resistance profile, especially the classes of beta-lactams, quinolones, macrolides, and sulfonamides and the producers of ESBL, MBL, and carbapenemase enzymes. In the Gram-positive bacteria, MRSA and VRE stood out with resistance to the other analyzed classes.

The use of corticosteroids in COVID-19 presents controversies, which include positive aspects in symptomatic control and negative aspects with regard to their use in critically ill patients, affecting the increase in mortality rates and modification of the lymphocyte population, predisposing individuals

Chart 1 – Highlighted results per study according to the investigation of multidrug-resistant bacterial coinfections and/or superinfections in patients diagnosed with COVID-19 admitted to hospital units.

Authors	Material analyzed; tests performed	Gender/age	Type of infection evidenced	Moment of bacterial detection	Bacteria identified and resistance profile	Total patients/ outcome
Qu et al.(35): level of evidence 2; country of origin was China.	Sputum and bronchoalveolar lavage fluid samples for genetic, phenotypic and transcriptomic sequencing.	Not included.	Superinfection.	When the patient was already seriously ill from COVID-19.	*P. aeruginosa* with resistance genes against aminoglycosides, beta-lactams, fosfomycin, and phenicol drugs.	One patient was included in the study. The ending is not included.
Moretti et al.(22): level of evidence 3; country of origin was Belgium.	Patient's record; statistical analysis.	72% were men/ median age was 62 years.	Superinfection.	Mean of 16 days after ICU admission and 13 days after intubation.	*K. pneumoniae* and *K. oxytoca* ESBL producers; *P. aeruginosa* producer of *Verona integron-encoded metallo-beta-lactamase* (VIM), susceptible only to aztreonam.	31 patients/17 died.
Bardi et al(23): level of evidence 3; country of origin was Spain.	Electronic medical record; statistical analysis.	77% were men/ median age was 61 years.	Superinfection.	Mean of 9 days after ICU admission.	Methicillin-resistant *Staphylococcus aureus* (MRSA).	140 patients/51 died.
Gaibani et al.(24): level of evidence 3; country of origin was Italy.	Bronchoalveolar lavage samples, culture and genetic sequencing; statistical analysis.	71% were men/ median age was 68 years.	Superinfection.	Not included.	*A. baumannii* resistant to carbapenems.	24 patients/8 died.
Kubin et al.(25): evidence level 3; country of origin was the United States of America (USA).	Electronic medical record; statistical analysis.	290 were men/ median age was 67 years.	a) Coinfection; b) Superinfection.	If coinfections, up to 72 h after admission; if superinfection from 4 to >28 days.	Enterobacteriaceae resistant to ceftriaxone and carbapenems (a, b); vancomycin resistant *Enterococcus* (a, b); MRSA (a,b).	516 patients/168 died.
Lardaro et al.(33): level of evidence 3; country of origin was the USA.	Electronic medical record; statistical analysis.	50.4% of the individuals included were women/mean age was 62.8 years.	Coinfection.	24–72 h after hospital admission.	Methicillin-resistant *S. epidermidis*.	6 patients/all were discharged from hospital.
Falcone et al.(26): level of evidence 2; country of origin was Italy.	Prospective follow-up of patients with SARS-CoV-2 pneumonia; statistical analysis.	73.9% were men/ median was 71 years of age.	Superinfection.	From 11 to 29.75 days of hospital stay.	Enterobacteriaceae producing ESBL, NDM, and KPC; methicillin-resistant MRSA and ScoN.	69 patients were included in the study/13 died.
Nori et al.(27): level of evidence 3; country of origin was the USA.	Laboratory information system and electronic medical record data; statistical analysis.	59% were men/ median was 62 years of age.	Coinfection.	Mean 6 days after SARS-CoV-2 result for respiratory cultures and 7 days for blood cultures.	NDM-producing Enterobacteriaceae; MRSA.	152 patients/42 admitted at the time of analysis; 24 high; 86 deaths.

Continue...

Chart 1 – Continuation...

Authors	Material analyzed; tests performed	Gender/age	Type of infection evidenced	Moment of bacterial detection	Bacteria identified and resistance profile	Total patients/ outcome
Farfour et al.(36): evidence level 4; country of origin was France.	Bronchial sample, rectal swab; cultures, antimicrobial susceptibility tests and genetic sequencing.	Not included.	Superinfection.	March 22 to April 30, 2021.	NDM-5-producing Enterobacteriaceae. Resistance genes against aminoglycosides, beta-lactams and quinolones were identified.	Six patients/ one admitted at the time of analysis and five discharged from hospital.
Hosoda et al.(34): level of evidence 5; country of origin was Japan.	Sputum, blood and laboratory parameters; culture and genetic virulence profile.	Only one woman patient aged 87 years.	Coinfection	From the samples collected on the seventh day of hospitalization.	Ampicillin-resistant *K. pneumoniae*.	One patient/ death from respiratory failure on the 9th day of hospitalization
Sharifipour et al.(28): level of evidence 2; country of origin was Iran.	Endotracheal samples in four stages, repeated at an interval of approximately three days; culture, biochemical and antimicrobial susceptibility tests.	11 men and 8 women; age ranged from 38 to 92 years, with a mean age of 62.1 years.	Superinfection.	From the 2nd to the 27th day of ICU admission.	*A. baumannii* producing MBL and sensitive only to colistin with a rate of 48%; MRSA sensitive only to tetracycline and vancomycin.	19 patients/18 died and 1 was discharged from hospital.
Kampmeier et al.(37): level of evidence 3; country of origin was Germany.	Blood, pleural drainage, and anorectal smear samples; culture and antimicrobial susceptibility testing.	Not included.	Superinfection.	23 to 26 days after entering the services.	Vancomycin resistant *Enterococci* (VRE).	3 patients included/outcome not reported.
Mohamed et al. (29): evidence level 5; country of origin was the USA.	Sputum and blood samples; culture and antibiogram.	Only one man patient aged 64 years.	Superinfection.	On the fifth day of hospitalization.	*S. maltophilia* sensitive only to trimethoprim/sulfamethoxazole and levofloxacin.	One patient/death on the twelfth day of hospitalization
Montrucchio et al.(30): level of evidence 4; country of origin was Italy.	Rectal swab; cultures, and genetic and antimicrobial susceptibility tests.	Four men and three women; median age of 54 years.	a) Coinfection; b) Superinfection.	Mean of 13 days after hospital admission and 12 days in relation to the ICU.	*K. pneumoniae* ESBL-producing *K. pneumoniae* carbapenemase-producing	Seven patients/ two died.
Cataldo et al.(31): level of evidence 3; country of origin was Italy.	Rectal swab; calculations and analysis of incidence of bloodstream infections.	41 men/mean age of 62 years.	Superinfection.	Mean 13 days after ICU admission (range 3 to 34 days).	*Pseudomonas spp.* piperacillin/ tazobactam and carbapenem resistant; VRE; ESBL-producing Enterobacteriaceae.	57 patients/18 deaths occurred.
Ramadan et al.(32): level of evidence 2; country of origin was Egypt.	Blood samples, sputum, endotracheal aspirates; culture, genetic tests, antibiogram, and statistical analysis.	144 men; 51 to 70 (36.2%) was the most common age group.	Coinfection	Between 1 and 7 days after the onset of COVID-19 symptoms.	Gram-positives were resistant to some beta-lactam antibiotics, aminoglycosides, and quinolones. Gram-negative bacteria were ESBL, CTX-M, NDM-1, and KPC producers.	260 patients/24 deaths occurred.

Source: Own elaboration, 2021.

to superinfections. Similarly, the use of immunomodulators brought benefits in terms of symptoms, but they were also participants in episodes of severe fungal and bacterial infections(39). In agreement, the sampling of this study indicated the use of corticosteroids and/or immunomodulators by the population studied and evidenced multidrug-resistant bacterial infections with an emphasis on episodes of superinfection associated with Gram-negative bacteria(22-27,29-31,34).

The use of antibiotics prior to infections was a reality in 7 of the 16 sampling studies. It is known that empirical antibiotic prescriptions were more frequent in this pandemic and that may result in their inappropriate use and development of multidrug-resistant agents, with additional cases of self-medication in addition to this calculation. Chen et al.(41) recommended its use in empirical treatment according to the clinical symptoms of patients with COVID-19, early identification of the bacterial agent, guidelines and local susceptibility tests, and applying the correct agents to sensitive species. Vellano and Paiva(42) narrated that procalcitonin can be an important biomarker in the use of antibiotics in COVID-19, because it allows to differentiate and confirm the bacterial pathogenic action. The authors also describe the consequent inflammatory storm resulting from the consumption of antibiotics in the absence of bacteria. While Mason et al.(43), through the hypothesis that the white blood cell count and C-reactive protein are able to distinguish a community-associated pneumonia from COVID-19, showed that both parameters decreased after antibiotic therapy in the first case, the same does not occur for COVID-19. It is worth noting that this is a more extensive subject than our work set out to explore, but others have given it more attention(6,7,44-46).

In addition to the use of medications capable of influencing the host's immune response and microbiota, there is still the important role of SARS-CoV-2 in relation to the host's immune system and bacterial populations. In this sense, there may be a decrease in the set of lymphocytes, in the diversity of intestinal bacteria, and an increase in opportunistic pathogens in patients with COVID-19, an aspect capable of favoring progression and negative prognosis if a second pathogen is concomitant or superimposed on the infection initial, demanding other measures for the restoration of the individual's health and impacting on mortality rates(3,41).

Coinfection cases in COVID-19 may require more intensive care and superinfection cases influence the length of stay and mortality rate(47). In critically ill patients, different invasive procedures are used with the objective of optimizing their prognosis; however, they are risk factors for the manifestation of different microorganisms; in sampling, for example, venous extracorporeal membrane oxygenation, pneumonia associated with invasive mechanical ventilation, and catheter-related and urinary tract infections stood out.

Regarding the multidrug-resistant bacteria described in our results, some other studies(48-50) highlight the important role of multidrug-resistant Gram-negative bacteria in COVID-19, concomitantly or secondarily, and the importance of outbreak prevention and control through adequate hand and environmental hygiene by employees and the proper use of personal protective equipment and surveillance cultures; in them, multidrug-resistant *E. coli*, *P. aeruginosa*, *A baumannii*, and *Klebsiella* spp. were identified. In contrast, Ripa et al.(51) highlighted the presence of Gram-positive bacteria, especially in bloodstream infections, highlighting MRSA and VRE.

Limitations

The first corresponds to the generalization of data from studies from different methodologies and countries without affecting the quality of the texts listed, which implies caution and limitation in the possibility of combining the data. The second corresponds to the lack of analysis of the incidence, prevalence, and lethality of coinfections and superinfections caused by multidrug-resistant bacteria in patients with COVID-19, since our methodological design did not include this approach. Finally, a gap was also left related to the prevention and control measures associated with multidrug-resistant bacteria in the health scenario of COVID-19.

CONCLUSION

This IR of the literature highlighted that multidrug-resistant Gram-negative bacteria were more participants in coinfections and superinfections in COVID-19 with the intersection of *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii* participation in these events and more others highlighted in each case. Thus, classes such as beta-lactams, quinolones, macrolides, and sulfonamides were mainly affected, and ESBL, MBL, and carbapenemase enzymes were proved to be important modulators of the resistance profile of the pathogens listed in this search. MRSA and VRE were the most common among the Gram-positive bacteria, especially in superinfections, and there was also resistance to the other classes analyzed in the sample.

Funding: none.

Conflicts of interests: the authors declare that there is no conflict of interest.

Authors' contribution: ARPF: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **AN:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **LMJM:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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