

Review Article

**Frequency of multidrug-resistant
microorganisms associated with bacterial
coinfections in hospitalized patient with covid-
19: A literature review**

UNDER PEER REVIEW

ABSTRACT

Patients with COVID-19 may be at risk of associated bacterial co-infections, and the involvement of multidrug-resistant (MDR) microorganisms in these cases can lead to an increase in morbidity and mortality rates. The objective of this study was to describe the frequency of the main MDR microorganisms associated with bacterial co-infections in patients hospitalized with COVID-19. To this end, we carried out a search in the PubMed and Regional Portal of the Virtual Health Library (VHL) databases, from December 2019 to September 2023, with the keywords COVID-19, co-infection and multidrug-resistant microorganism. Of the 535 articles initially found, only 14 were selected. Gram-negative bacteria were most frequently involved in bacterial co-infections in patients with COVID-19 (70%). Among these, *Klebsiella pneumoniae* and *Acinetobacter baumannii* predominated, with 85.71% and 78.57%, respectively. Among gram-positive bacteria, *Staphylococcus aureus* (71.42%) was the most common. Among MDR microorganisms, the prevalent species were carbapenem-resistant gram-negative bacilli (32%) and methicillin-resistant *S. aureus* (85.7%). Furthermore, a higher frequency of MDR microorganisms was observed in patients with COVID-19 in intensive care units (ICU). Thus, the findings of the present study indicate the need for attention to infections caused by multidrug-resistant microorganisms in critically ill patients with COVID-19.

Keywords: COVID-19; Bacterial co-infections; Multi-resistant microorganisms.

1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a clinical condition caused by the novel coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), previously known as 2019-nCoV. Belonging to the Coronaviridae family, it is a zoonotic RNA virus that first emerged in late 2019 in Wuhan, China, with the hypothesis of bats and the Malayan pangolin as potential sources due to the genetic proximity between CoVs found in these animals and the current virus⁽¹⁻³⁾. It primarily infects the respiratory system and is transmitted through respiratory droplets via close contact, leading to a spectrum of illness ranging from mild to critical conditions requiring specialized treatment in intensive care units⁽⁴⁾.

Reports of secondary infections associated with COVID-19 have become increasingly common. The presence of other microorganisms, such as bacteria, fungi, and viruses, is a critical factor that can complicate the diagnosis, prognosis and treatment of the disease, as well as exacerbate and increase morbidity and mortality⁽⁵⁾. Coinfection is defined as the result of two or more infectious agents acting simultaneously^(6,7). For cases of patients diagnosed with COVID-19 who have coinfections with other respiratory pathogens, the immediate administration of antibiotics in accordance with antimicrobial susceptibility reports, as well as strict infection control strategies, are essential to reduce severity, complications, mortality, and the nosocomial transmission facilitated by these superbugs⁽⁸⁾.

The emergence of infections caused by multidrug-resistant microorganisms (MDRs) has become a health risk, since uncontrolled infections in the hospital setting can prolong patients' hospitalization period by complicating their clinical status and recovery⁽⁹⁾.

The World Health Organization (WHO) defines healthcare-associated infection as "an infection occurring in a patient during the process of care in a hospital or other healthcare facility that was not present or incubating at the time of admission"⁽¹⁰⁾. Nosocomial infections can also encompass those that manifest within 72 hours of admission when associated with diagnostic and therapeutic procedures performed during this period⁽¹⁰⁾.

Nosocomial infection is an event detected based on clinical and laboratory data, with the time frame varying depending on the patient's care unit. In intensive care units (ICUs), for example, the timeframe extends up to 48 hours after discharge⁽⁶⁾.

Over the last decade, antibiotic resistance has become one of the major global public health concerns due to the emergence of pathogens with new resistance mechanisms. Antimicrobial resistance is a growing crisis that affects global health and demands urgent action⁽¹¹⁾. Multidrug-resistant bacteria are microorganisms that are not susceptible to at least one antibiotic from three or more classes of antibiotics. They usually arise due to improper use of antimicrobials or their uncontrolled spread through contamination vectors, posing difficulties to clinical treatment⁽¹²⁾.

Therefore, considering the relevance of multidrug-resistant bacteria in healthcare and aiming to highlight their role in the pandemic scenario, we aimed to describe the frequency of the main MDR microorganisms associated with bacterial coinfection in hospitalized patients with COVID-19, based on the literature from December 2019 to September 2023.

2. MATERIAL AND METHODS

This is an integrative literature review that utilized scientific literature to analyze the prevalence of multidrug-resistant microorganisms in hospitalized patients with COVID-19 during the period from December 2019 to September 2023. Its methodological structure consists of six vital phases, following the procedures described by Souza *et al.*⁽¹³⁾.

In the first phase, the guiding question used to steer the research was: "Which multidrug-resistant bacteria have been prevalent in hospitalized patients with COVID-19?"

In the second methodological phase, we conducted searches in the PubMed and Regional Portal of the Virtual Health Library (BVS) databases for scientific articles published between December 2019 and September 2023. The keywords used were: COVID-19, Bacterial Coinfection, and Multidrug-Resistant Microorganism. Boolean operators "and" and "or" were used as search tools, combining Health Sciences Descriptors (DeCS) in the regional BVS portal, resulting in: ("COVID-19") and ("coinfection") and ("bacteria or multiresistant") along with language filter (English) and publication year (2019 or 2023). The same combinations were used for MeSH (Medical Subject Headings) in PubMed searches, resulting in: ("COVID-19") AND ("coinfection") AND ("bacteria" OR "multidrug resistance"). The articles were directly related to the years 2019 to 2023, so no additional filters were necessary.

Each of the retrieved articles was analyzed according to the inclusion and exclusion criteria. Inclusion criteria were: the period between December 2019 and September 2023, studies investigating bacterial coinfection in hospitalized patients with COVID-19, studies reporting coinfection with multidrug-resistant bacteria, articles in English or Portuguese, and articles that addressed the guiding question. Exclusion criteria were: articles that did not address the research question, articles focused on coinfections with other specific microorganisms that were not bacteria, duplicates, literature reviews, and letters.

In the third phase, an adapted instrument from Souza *et al.*⁽¹³⁾ was used for data extraction and recording of selected articles. This instrument was structured with the following topics: article title, authors, year of publication, country, gender, age, department, material analyzed, prevalent bacteria, and sample size/outcome. An Excel spreadsheet was created for data storage and organization.

The fourth phase involved analysis of the selected articles. Titles and abstracts were read, and inclusion and exclusion criteria were applied to select the articles that were read in full.

The fifth phase involved the description and discussion of the results. Subsequently, in the sixth phase, the review was written.

3. RESULTS

Initially, 535 articles were found as result of the search in the databases using the associated descriptors and keywords. After analyzing the inclusion and exclusion criteria, 14 articles were chosen: 10 were identified in PubMed and 4 in the BVS Regional Portal (Figure 1). Of these, 37.71% (5/14) corresponded to the year 2023, and 37.71% (5/14) to 2022, with the remaining ones pertaining to 2021 and 2020. Additionally, 50% of the studies were conducted in Asia, followed by 29% in Europe, and the remainder in Africa.

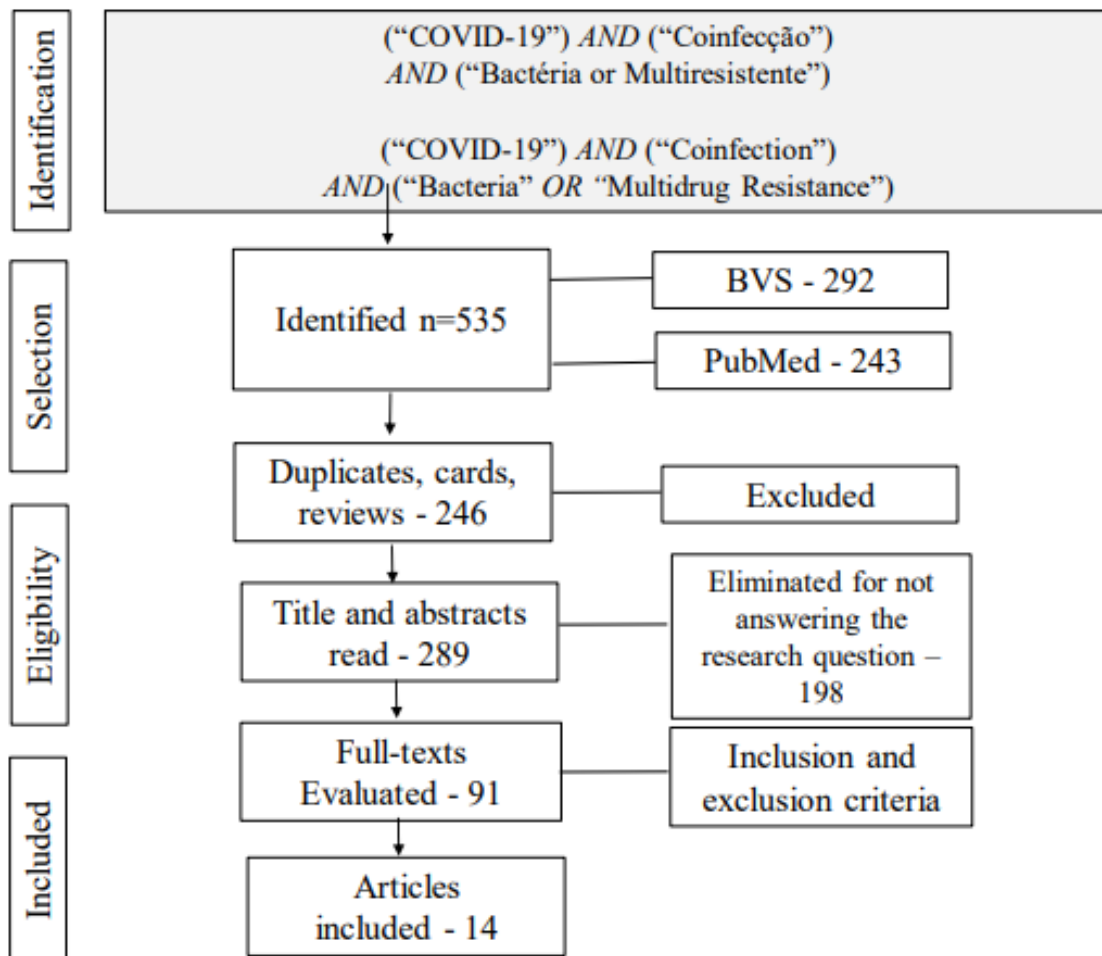


Figure 1 - Flowchart of the search and selection procedure of the articles included in the sample.

Twelve studies had more male patients, while the majority were female in only one study⁽¹⁴⁾, and in another study the gender of the patients was not identified⁽²⁷⁾. The median age of the studied populations was similar, ranging from 50 to 70 years old. Regarding the ward where the patients were hospitalized, 71.42% were in intensive care units (ICUs)^(14,16,17,19-24,27). In all articles, the analyzed material was collected from electronic patient record management systems. Ten studies provided details about the types of clinical samples cultured, including sputum, blood and urine, while four study did not specify the source of the sample, indicating only "patient record analysis"^(16,17,19,22).

Regarding the occurrence of multidrug-resistant microorganisms (MDRs) in coinfections, gram-negative bacteria accounted for 70%. Among them, *Klebsiella pneumoniae* and *Acinetobacter baumannii* predominated with 85.71% and 78.57%, respectively. Among gram-positive bacteria (30%), *Staphylococcus aureus* was the most frequent at 71.42%⁽¹⁵⁻²⁶⁾. Among MDR microorganisms, the most frequently isolated species were carbapenem-resistant gram-negative bacilli (32%), followed by methicillin-resistant *S. aureus* (10%) among gram-positive bacteria.

The sample size varied from study to study, and the number of deaths was not reported in some articles. The most common comorbidities among the participants in the different studies were diabetes mellitus, systemic arterial hypertension, kidney disease, and respiratory diseases⁽¹⁴⁻²⁷⁾. Most patients received empirical antibiotic therapy upon admission to the ICU.

Table 1 presents a list of the selected articles from the databases, describing the article title, authors, year of publication, country, gender, age, hospital sector, material analyzed, prevalent bacteria, and sample size/outcome

Table 1. Highlighted Results by Study for the Investigation of Bacterial Coinfections by MDR Microorganisms in Patients Diagnosed with COVID-19 Hospitalized in Healthcare Units.

Title	Author/Year of Publication/Country	Gender/age	Sector	Material Analyzed	Prevalent Bacteria	Total Patients/Outcome
Characteristics and Risk Factors of Secondary Bacterial Infections in Patients with COVID-19 ⁽¹⁴⁾	Wu <i>et al.</i> ; 2023; China.	51.2% were female; average age of 68 years.	ICU; others.	Blood, urine, and sputum cultures; data extracted from the electronic patient record management system.	<i>Acinetobacter baumannii</i> ; <i>Klebsiella pneumoniae</i> ; <i>Escherichia coli</i> ; <i>Enterococcus faecium</i> ; <i>Staphylococcus aureus</i> (MRSA)	43; not specified.
Bacterial Coinfection at Hospital Admission in Patients with COVID-19 ⁽¹⁵⁾	Moreno-García <i>et al.</i> ; 2022; Spain.	64.5% were male; average age of 54 years.	Not specified.	Blood cultures; urinary antigen test (pneumococcal); sputum culture; patient record data.	<i>Streptococcus pneumoniae</i> ; <i>Pseudomonas aeruginosa</i> ; <i>Staphylococcus aureus</i> ; <i>K. pneumoniae</i> ; <i>E. coli</i>	122; not specified
Coinfection and Superinfection in Critically Ill ICU Patients with Severe Pneumonia due to COVID-19 and Influenza Pneumonia: Are the Profiles Different? ⁽¹⁶⁾	Chen <i>et al.</i> ; 2023; China.	80.5% were male; average age of 69 years.	ICU	Electronic patient record management system.	<i>P. aeruginosa</i> ; <i>A. baumannii</i> ; <i>K. pneumoniae</i> ; <i>S. aureus</i> ; <i>Enterococcus faecium</i>	27; not specified
Epidemiology of Bacterial Coinfections and Risk Factors in Patients Hospitalized for COVID-19 in Spain: A National Study ⁽¹⁷⁾	López <i>et al.</i> ; 2020; Spain.	66.55% were male; average age of 67 years.	ICU	Patient records.	<i>Pseudomonas</i> spp.; <i>S. pneumoniae</i> ; <i>Staphylococcus</i> spp.; <i>S. aureus</i> ; <i>Streptococcus</i> spp.; <i>Enterococcus</i> spp.	4,754; 1,590 deaths.
Incidence of Coinfections and Superinfections in Hospitalized Patients with COVID-19: A Retrospective Cohort Study ⁽¹⁸⁾	García-Vidal <i>et al.</i> ; 2020; Spain.	55.8% were male; average age of 62 years.	Not specified.	Clinical samples of sputum, blood cultures, urine cultures, urinary antigen tests; data extracted from patient records.	<i>P. aeruginosa</i> ; <i>E. coli</i> ; <i>K. pneumoniae</i> ; <i>S. aureus</i> ; <i>S. pneumoniae</i>	61; 13 deaths.
	Russo <i>et al.</i> ; 2022;	66% were male;	ICU	Patient records and	<i>Acinetobacter baumannii</i>	32; 26 deaths.

Title	Author/Year of Publication/Country	Gender/age	Sector	Material Analyzed	Prevalent Bacteria	Total Patients/Outcome
Multidrug-Resistant Infections by <i>Acinetobacter baumannii</i> in COVID-19 Patients Hospitalized in ICU ⁽¹⁹⁾	Italy.	average age of 62 years.		in hospital computerized databases.	multidroga resistente (MDR-AB).	
Bacterial Infections Associated with COVID-19 in the Intensive Care Unit: A Case-Control Study ⁽²⁰⁾	Kaçmaz <i>et al.</i> ; 2023; Turkey.	60% were male; average age of 71 years.	ICU	Clinical samples detected by cultures and/or molecular tests in the first episode; data extracted from patient records.	<i>Staphylococcus</i> spp.; <i>Acinetobacter</i> spp.; <i>Klebsiella</i> spp.; <i>P. aeruginosa</i>	67; 18 deaths.
Secondary Infections in Critically Ill Patients with COVID-19-Associated ARDS in the ICU: Frequency, Microbiological Characteristics, and Risk Factors ⁽²¹⁾	Taysi <i>et al.</i> ; 2023; Turkey	50.8% were male; average age of 70 years.	ICU	Clinical samples of sputum and tracheal aspirate; blood culture and urine culture; data extracted from patient records.	<i>Klebsiella</i> spp.; <i>A. baumannii</i> ; <i>E. coli</i> ; <i>P. aeruginosa</i> ; <i>S. aureus</i> ; <i>Enterobacter aerogenes</i>	61; not specified.
The Impact of the COVID-19 Pandemic on Healthcare-Associated Infections: A University Hospital Experience ⁽²²⁾	Obeidat <i>et al.</i> ; 2023; Jordan.	82% were male, average age of 72 years.	ICU; others.	Patient records.	<i>A. baumannii</i> ; <i>E. coli</i> ; <i>K. pneumoniae</i> ; <i>P. aeruginosa</i> ; <i>S. aureus</i>	17; 15 deaths.
Profile of Coinfections and Secondary Infections in COVID-19 Patients at a COVID-19 Dedicated Facility in an Indian Tertiary Care Hospital: Implications for Antimicrobial Resistance ⁽²³⁾	Khurana <i>et al.</i> ; 2021; India.	62.5% were male (ICU); 63% were male (Wards); average age of 50 years.	ICU (n= 56); Wards (n= 95).	Clinical samples of blood, urine, respiratory samples, pus; patient records.	<i>K. pneumoniae</i> ; <i>A. baumannii</i> ; <i>E. coli</i> ; <i>P. aeruginosa</i> .	151; 51 deaths.

Title	Author/Year of Publication/Country	Gender/age	Sector	Material Analyzed	Prevalent Bacteria	Total Patients/Outcome
Profiles of Bacterial Coinfection and Antibiotic Resistance among Hospitalized Patients with COVID-19 ⁽²⁴⁾	Bazaid <i>et al.</i> ; 2022; Saudi Arabia.	55% were male; average age 60 years.	ICU (n= 49); Wards (n= 24).	Clinical samples of blood, urine, sputum, and wound smears; patient records.	<i>K. pneumoniae</i> ; <i>A. baumannii</i> ; <i>P. aeruginosa</i>	73; not specified.
Preditores de gravidade e perfil de resistência à coinfeção em pacientes com COVID-19: primeiro relatório do Alto Egito ⁽²⁵⁾	Radaman <i>et al.</i> ; 2020; Egypt.	55.4% were male; the most common age range was 51 to 70.	Not specified.	Blood samples, sputum, endotracheal aspirates; culture, genetic tests, antibiogram, and statistical analysis.	<i>K. pneumoniae</i> ; <i>A. baumannii</i> ; <i>P. aeruginosa</i> ; <i>S. aureus</i> ; <i>S. pneumoniae</i> ; <i>E. faecalis</i>	260;24deaths.
Prevalence and Clinical Impact of Coinfection in Patients with Coronavirus Disease 2019 in Korea ⁽²⁶⁾	Jeong <i>et al.</i> ; 2022; South Korea.	51.4% were male; average age 70 years.	Not specified.	Clinical samples of sputum, nasal swab, and tracheal aspiration; patient records.	<i>A. baumannii</i> (CRAB); <i>P. aeruginosa</i> (CRPA); <i>S. aureus</i> (MRSA), <i>K. pneumoniae</i> ; <i>E. coli</i> . (produtoras de ESBL)	30; not specified.
A Comparative Study on Bacterial Coinfections and the Prevalence of Multidrug-Resistant Organisms among Patients in COVID and Non-COVID Intensive Care Units ⁽²⁷⁾	Sathyakamala <i>et al.</i> ; 2022; India.	Not specified.	ICU.	Clinical samples of blood, urine, and sputum; patient records.	<i>E. coli</i> , <i>Klebsiella spp.</i> ; <i>Pseudomonas spp.</i> ; <i>Acinetobacter spp.</i> ; <i>Citrobacter spp.</i> ; <i>Proteusspp.</i>	203; not specified.

Source: Authors, 2023

4. DISCUSSION

Microbial coinfection plays a significant role in the occurrence and development of SARS-CoV-2 infection, increasing the challenges in diagnosing, treating, and predicting COVID-19, and even exacerbating the disease's symptoms and mortality⁽²⁸⁾.

In this study, the rate of bacterial coinfection ranged from 9.6% to 29.8%. Ripaet *et al.*⁽²⁹⁾ found a coinfection rate of 9.3% in hospitalized COVID-19 patients. Yu *et al.*⁽³⁰⁾ investigated the rate of secondary infection in 226 critically ill COVID-19 patients, and found a coinfection rate of 21.7%. A meta-analysis conducted in 2020 concluded that 7% of patients had bacterial coinfection, a rate that increased to 14% for patients admitted to the ICU⁽³¹⁾. Huang *et al.*⁽³¹⁾ reported that four cases (9.8%) had secondary bacterial infections among 41 hospitalized COVID-19 patients. In the case of COVID-19 coinfections, the mechanisms leading to a low incidence are not well understood. Several hypotheses have been raised, including prophylactic antibiotic therapy upon hospital admission and the presence of an immune factor such as macrophage hyperactivation⁽³³⁾.

The results of this study showed that bacterial coinfections can affect the progression of COVID-19 and mortality, especially in patients in intensive care units (ICUs)^(14,16,17,19-24,27). Other studies have reported similar results, with only 7% of hospitalized patients presenting bacterial coinfections and a high degree of heterogeneity, increasing to 14% in ICU patients^(34,35).

According to Sharifipouret *al.*⁽³⁶⁾, the observed prevalence of bacterial coinfection among COVID-19 patients in ICUs can be attributed to various factors, including compromised immunity, low adherence to self-protection measures by healthcare professionals and patients, weak infection control in wards, high workload, and staff shortages.

Additionally, we observed that the majority of COVID-19 patients with coinfections were male, reaching up to 80% in some studies^(16,22). Studies suggest that most coinfections involve male patients, which is an additional independent risk factor in the more severe cases of this condition, in addition to the major comorbidities and the use of immunosuppressive medications that favor this outcome⁽³⁷⁻³⁹⁾.

Regarding the prevalent microorganisms found in hospitalized COVID-19 patients in our study, gram-negative bacteria stood out (70%), among which *Klebsiella pneumoniae* (85.71%) and *Acinetobacter baumannii* (78.57%) predominated^(14-16,18-27). Among gram-positive bacteria, *Staphylococcus aureus* had the highest frequency at 71.42%^(14-17,18,20-22,25,26), followed by *Streptococcus pneumoniae* (35.71%)^(15,17,18,25). In line with these findings, Obeidat *et al.*⁽²²⁾ reported, in a study involving the distribution of reported microorganisms, that gram-negative and gram-positive bacteria were isolated in 72% and 8.5% of cases, respectively. This finding differed from a Chinese study, where gram-negative bacteria accounted for 87.5%, and gram-positive isolates were identified in 12.0% of cases⁽⁴⁰⁾.

A study conducted in Bahrain demonstrated the prevalence of gram-negative isolates in over 1,380 COVID-19 patients, distributed as follows: *Klebsiella pneumoniae* (23.8%), *Pseudomonas aeruginosa* (23.2%), *Acinetobacter baumannii* (22.0%), and *Escherichia coli* (17.1%)⁽⁴¹⁾. Furthermore, among 1,495 COVID-19 patients hospitalized in Wuhan with secondary bacterial infections, the most commonly isolated bacteria were *Acinetobacter baumannii* (35.8%) and *Klebsiella pneumoniae* (30.8%)⁽⁴²⁾. Conversely, an international retrospective study showed that gram-positive bacteria were the most commonly isolated microorganisms in COVID-19 patients, with *Streptococcus pneumoniae* and *Staphylococcus aureus* each occurring in 16.2% of patients. These studies suggest that drug resistance and the distribution of these pathogenic microorganisms vary among countries⁽²²⁾.

In this integrative review, multidrug-resistant microorganisms were reported in 85.7% of cases. The most frequently isolated species were carbapenem-resistant gram-negative bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA). The most prevalent resistant microorganisms in the analyzed studies were methicillin-resistant *Staphylococcus aureus* (MRSA; 64.00%), followed by carbapenem-resistant *Acinetobacter baumannii* (CRAB; 57.14%) and extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* (ESBL+; 42.85%). However, in the study by Mahmoudi⁽⁴³⁾ and the one conducted by Khurana *et al.*⁽⁴⁴⁾, there were higher occurrences of multidrug-resistant species of *Klebsiella*, followed by *Acinetobacter* spp. On the other hand, the study by Rezasoltaniet *al.*⁽⁴⁵⁾ observed a higher prevalence of *Staphylococcus aureus* (MRSA).

Obeidat *et al.*⁽²²⁾ reported several resistance mechanisms among microorganisms. However, extended-spectrum beta-lactamase (ESBL) production was the leading cause of antimicrobial resistance among *Klebsiella* spp. and *E. coli*,

reaching 67% and 52%, respectively. Moreover, a high occurrence of carbapenem-resistant gram-negative bacteria was observed, with 97% for *A. baumannii* (CRAB) and 44% for *P. aeruginosa*. This fact certainly is important and can lead to severe complications in cases of coinfection in COVID-19 patients. Although these data are higher than those reported in a Chinese study, where the rates of occurrence of coinfections by *E. coli* (ESBL), *K. pneumoniae* (ESBL), *A. baumannii* (CRAB), and *P. aeruginosa* (CRO) were 30.5%, 16.1%, 19.5%, and 10.0%, respectively⁽⁴⁶⁾.

The extensive use of broad-spectrum antimicrobial drugs during the COVID-19 outbreak in hospitalized patients, especially in ICUs, may have contributed to the selection of pathogens with different resistance profiles. Additionally, microorganisms such as *S. aureus*, *Enterococcus* spp., Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter* spp. are often responsible for healthcare-associated infections and are prone to developing multidrug resistance.

5. CONCLUSION

[This integrative literature review found that patients hospitalized in ICUs with COVID-19 who presented bacterial coinfection were more frequently infected by multidrug-resistant microorganisms in comparison with patients admitted to other hospital wards/sectors. The microorganisms most frequently isolated in these individuals with a multidrug resistance profile were *A. baumannii* (CRAB), *K. pneumoniae*, *E. coli* (ESBL), and *P. aeruginosa* (CRO). Additionally, among gram-positive bacteria, *S. aureus* (MRSA) stood out. Therefore, it is important to emphasize that bacterial coinfections in critically ill patients should not be underestimated. These results indicate the need to pay attention to infections caused by multidrug-resistant microorganisms, and reinforce the need for ethical and rational use of antibiotics.

CONSENT (WHEREEVER APPLICABLE)

No manuscripts will be peer-reviewed if a statement of patient consent is not presented during submission (wherever applicable).

This section is compulsory for medical journals. Other journals may require this section if found suitable. It should provide a statement to confirm that the patient has given their informed consent for the case report to be published. Journal editorial office may ask the copies of the consent documentation at any time.

Authors may use a form from their own institution or SDI Patient Consent Form 1.0. It is preferable that authors should send this form along with the submission. But if already not sent during submission, we may request to see a copy at any stages of pre and post publication.

If the person described in the case report has died, then consent for publication must be collected from their next of kin. If the individual described in the case report is a minor, or unable to provide consent, then consent must be sought from their parents or legal guardians.

Authors may use the following wordings for this section: "All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal."

ETHICAL APPROVAL (WHEREEVER APPLICABLE)

This section is compulsory for medical journals. Other journals may require this section if found suitable. If human subjects are involved, informed consent, protection of privacy, and other human rights are further criteria against which the manuscript will be judged. It should provide a statement to confirm that the authors have obtained all necessary ethical approval from suitable Institutional or State or National or International Committee. This confirms either that this study is not against the public interest, or that the release of information is allowed by legislation.

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