Superinfections in a Cohort of Patients with COVID-19 Admitted to Intensive Care: Impact of Gram Negative Resistance.

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Research Article

Abstract

Background: some studies have shown that superinfection during pandemics may have contributed to high mortality. Our objective is to identify the frequency, types and aetiology of superinfections in patients with Covid-19 admitted to the intensive care unit (ICU) and to evaluate the results of ICU stay, duration of mechanical ventilation (MV) and hospital mortality.

Methods: retrospective cohort of adult patients admitted to the ICU for more than 48 hours between March to May 2020. Comparisons of groups with and without ICU- acquired infection were established.

Results: a total of 191 patients with laboratory-confirmed COVID-19 were included and 57 patients had 97 secondary infectious events. Most frequent agents were *Acinetobacter baumannii* (28.9%), *Pseudomonas aeruginosa* (22.7%) and *Klebsiella pneumoniae* (14.4%); multi-drug resistance was present in 96% *Acinetobacter* and in 57% *K.pneumoniae*. The most prevalent infection was ventilator-associated pneumonia (VAP) in 57.9% of patients with bacterial superinfection, or 17.3% of all COVID-19 patients admitted to ICU, followed by tracheobronchitis, in 26.3%. Patients with superinfection had a longer ICU stay (40.0 vs. 17; $p < 0.001$), as well as a longer duration of MV (24.0 vs 9.0; $p = 0.003$). There were 35.6% deaths overall, of which 39.7% of the patients had superinfection; in those who survived, 24.4% had a superinfection (OR 2.041; 95% CI 1.080–3.859).

Conclusion: a high incidence of superinfections was seen, mostly caused by Gram-negative bacteria. The most common infection was VAP. Superinfections were associated with longer ICU stay and MV use and higher mortality.

Introduction

The disease caused by the new coronavirus (Covid-19) has already affected more than 116 million people in more than 180 countries and has caused at least 2.5 million deaths. Brazil is the third country with the most cases in the world and the second with the highest number of fatalities [1].

Some studies have shown that secondary infections during pandemics may have contributed to high mortality [2]. A review of samples from influenza victims from 1918–1919 showed that most deaths probably resulted directly from secondary bacterial pneumonia caused by common upper respiratory tract bacteria [3]. During the *influenza A* pandemic in 2009, bacterial complications were present in approximately 1 out of 4 severe or fatal cases, with greater morbidity in adults and patients admitted to the Intensive Care Unit (ICU) [4].

Although the clinical profile and mortality rate of patients with severe Covid-19 have been previously published [5–7], infections acquired in the hospital, related to healthcare, are still little known and knowledge may contribute to better results in clinical management and outcomes.

The primary objective of this study is to identify the incidence, etiology and types of ICU-acquired superinfections in patients with Covid-19 in a hospital in Rio de Janeiro. The secondary objective is to assess length of stay in the ICU, duration of mechanical ventilation and hospital mortality in this population.

Methodology

Study design

Our study was designed as a retrospective cohort of patients admitted consecutively to the intensive care unit. The methods, as well as the statistical analyzes, followed appropriate regulations and guidelines.

A single-center study was conducted in a private hospital in the city of Rio de Janeiro, Brazil, by consulting the electronic medical records of adult patients consecutively admitted to the ICU diagnosed with Covid-19 confirmed by reverse transcription-polymerase chain reaction from a nasopharyngeal swab [8]. The study period was 17 March to 27 May 2020.

Population

Patients were classified into two groups: the first, those with ICU-acquired superinfection and the other without, so as to assess the impact of superinfections on outcomes. All individuals had been in ICU for more than 48 hours and were 18 years old or older. Microbiologic studies and treatment decisions were not standardized and were made by attending physicians. All patients had received a third generation cephalosporin plus azithromycin, as per protocol for severe COVID-19 presentation at the time [9].

Microbiology

Bacterial cultures were obtained from blood, urine or respiratory samples using the BacT/Alert (Biomerieux, France) system, and pathogen identification was done by Vitek 2 (Biomerieux, France). Antimicrobial susceptibility testing was done by the standard disk-diffusion method in accord with the Clinical& Laboratory Standards Institute [10].

Definitions

Diagnoses of hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), central line-associated bloodstream infections (CLABSI) and catheter-associated urinary tract infection (CAUTI) followed the criteria of the *Centers for Disease Control and Prevention National Healthcare Safety Network* [11]. The modified Duke's criteria were used to diagnose infective endocarditis [12]. Multidrug resistance (MDR) was defined according to *European Centre for Disease Prevention and Control* e *Centers*

for Disease Control and Prevention [13]. Infectious episodes were considered as distinct events when different microorganisms were isolated following clinical or laboratory signs of infection, such as fever or hypothermia, increased CRP levels, or imaging studies.

Population characteristics

For description of the population, the following data were obtained: age, sex, body mass index - BMI (Kg/m^2), *Simplified Acute Physiology Score 3* (SAPS 3), presence of absence of systemic arterial hypertension (SAH), diabetes mellitus (DM), asthma, chronic obstructive pulmonary disease (COPD), coronary artery disease, left ventricular dysfunction, solid organ cancer, date of onset of symptoms, length of stay in the ICU, length of hospital stay and clinical complications (acute respiratory distress syndrome - ARDS, according to Berlin criteria [14], need for invasive ventilatory support, use of vasopressor drugs, presence of venous thromboembolism and death).

Data collection and interpretation of the relevance of culture results of biological samples were carried out by medical researchers LPMM and RABB. The divergences were resolved by consensus and, whenever necessary, by a third reviewer (CAE).

Statistical analysis

Continuous variables with normal distribution were expressed as means and standard deviations and continuous variables without normal distribution were expressed as medians and interquartile ranges; categorical variables were expressed as absolute values and relative frequency. Normality tests were performed using the Shapiro-Wilk model. Comparisons between continuous variables were performed using the unpaired Student's t test or the Mann-Whitney U test. For comparisons of categorical variables, the chi-square test was used. Logistic regression analysis was performed to determine the predictors of secondary infection. Variables that were associated with secondary infection at a significance level of p < 0.20 were included in the multivariate regression model. The stepwise forward method was used. The magnitude of the effect of each variable was estimated by calculating the odds ratio (OR) and their respective 95% confidence intervals (CI). The tests were two-tailed and the statistical significance was expressed as p < 0.05. The data were analyzed using SPSS 20.0.

Results

Occurrence of infections

A total of 191 adult patients were consecutively admitted to the ICU with a laboratory-confirmed diagnosis of Covid-19; the majority was male (60.7%) and median age was 70.5 years (58.5 – 80.1). Clinical features of all patients and of the groups with and without ICU-acquired superinfections are shown in table 1. The median time between hospital admission and infection was 17 days and 57

(29.8%) patients had 97 secondary infectious events. Most frequent agents were *Acinetobacter baumanii* (28/97; 28.9%), *Pseudomonas aeruginosa* (22/97; 22.7%) and *Klebsiella pneumoniae* (14/97; 14.4%); multi-drug resistance was present in 27/28 (96%) *Acinetobacter* and in 8/14 (57%) *K. pneumoniae*. At least 48 (49.5%) events were due to bacteria with some antimicrobial resistance profile. The most prevalent superinfection was VAP in 33/57 (57.9%) patients, or 33/191(17.3%) of all COVID-19 patients admitted to ICU, followed by tracheobronchitis, in 15 (26.3%) patients. Table 2 presents a comparison of patients who died with those who survived stratified by type of superinfection. Table 3 shows the etiological agents identified in ICU-acquired superinfections of 57 adult patients admitted due to COVID-19. The superinfections found were VAP (45/97; 46%), tracheobronchitis (21/97; 22%), CLABSI (17/97; 18%), CAUTI (6/97; 6.2%), HAP (5/97; 5.2%), osteomyelitis (2/97, 2.0%) and endocarditis (1/97; 1.0%). The median time from hospital admission to the occurrence of infection was 17 days (IQR 10 - 35.5 days).

Outcomes

Patients with superinfection had a longer ICU stay, in days, compared to patients without infection [40.0 (30.0 - 46.0) x 17.0 (11.0 - 26.0); p <0.001], as well as longer time on mechanical ventilation [24.0 (11.0 - 29.0) x 9.0 (5.0 - 15.0); p = 0.003]. There were 68/191 (35.6%) deaths overall and of these, 39.7% of the patients had some secondary infection, whereas in the group of survivors, only 24.4% had superinfection (OR 2.041; 95% CI 1.080 - 3.859; p = 0.0270). There was a greater distribution of VAP cases in the group of patients who died compared to those who survived (30.9% x 9.8%; OR 4.133; 95% CI 1.881 - 9.079; p <0.001), as shown in Table 2.

The bivariate analysis showed an association of superinfections with the following variables: SAPS 3, C-reactive protein level, use of corticosteroids in the ICU, moderate ARDS, hemodialysis, mechanical ventilation, use of vasopressors and duration of mechanical ventilation, as shown in table 4. However, the multivariate analysis showed an association with the SAPS 3 score only (OR 1.093; 95% CI 1.016 - 1.175; p = 0.017).

Discussion

In our retrospective observational cohort of 191 patients, we observed a high prevalence of infection acquired in the ICU and a predominance of Gram-negative bacteria, especially multirresistant *Acinetobacter* and *K. pneumoniae*. These data may reflect the challenges within an ICU dedicated to the care of patients with Covid-19, who, in order not to lose focus on maintaining life in the face of a new highly contagious disease without specific treatment, flows and protocols already established for the control of nosocomial infection had to be adapted dynamically, according to the local pandemic scenario. Few studies on secondary infection in the ICU have been published despite the fact it is an important topic for the management of critically ill patients with Covid-19. A meta-analysis of 3,448 patients assessed the prevalence of co-infection and secondary infection in patients with Covid-19 and

found 3.5% presence of co-infection and 15.5% of superinfection, with a greater proportion among the most severely ill individuals; interestingly, despite the low incidence of bacterial co-infection, more than 70% of patients received antimicrobials [15]. Moreover, as pointed out in a letter, self- administration of antibiotics was 33% among COVID-19 patients in Peru, and although there is some regulation in Brazil, this may have also been a contributing factor to selection of bacterial resistance in our patient cohort [16]. Therefore, not only infection control practices play a role in the acquisition of infection in ICU's during the COVID-19 situation, but antibiotic overuse selects multirresistant bacteria [15]. Ripa et al [17] showed that a secondary infection was seen in 9.3% of 731 patients hospitalized for COVID-19 in Italy. Incidence of healthcare related bacterial pneumonia in patients admitted due to COVID-19 was 0.4 per 1000 patient follow up days outside ICU vs 15.2 in ICU, that is, incidence was 37-fold higher in ICU. Gram negatives predominated in their study, of which *Acinetobacter* accounted for the greater portion (nearly a third). Risk factors for secondary infections on multivariate analysis were early need for ICU, respiratory failure and severe baseline lymphopenia. A report on patients with COVID-19 in 19 ICUs in China showed that carbapenem resistant Acinetobacter (CRAB) was identified in 19/30 isolates related to secondary infection, of which most were VAP. A CRAB outbreak during the COVID-19 pandemic has been reported in the USA [18]; the report states that responding to COVID-19 related care needs, changes such as less frequent patient bathing with chlorhexidine gluconate and a 43% reduction in ICU CRAB screening tests occurred; there were critical shortages for nursing and environmental services resulting from staff members' illness and quarantine. In Lille, France, an OXA-23-producing *Acinetobacter baumannii* outbreak occurred during the COVID-19 epidemy in their ICUs; CRAB was found in respiratory and blood samples taken from 21 patients, all of them on ventilation [19]. Environmental sampling was performed on equipment such as ECG devices, ultrasound scanner, hemodialysis machine, but the isolate was not recovered from these samples. A small Iranian study of 19 patients admitted to ICU, all on mechanical ventilation, showed that all patients acquired infection, and 17 of them had multirresistant *Acinetobacter* as the causative agent of VAP; mortality was 95% [20]. In Spain, of 712 patients hospitalized with COVID-19, 11% developed superinfection, and *Acinetobacter* sensitive to colistin only was the main pathogen in pneumonia and bloodstream infections, which was attributed to an outbreak at the time; the authors report that this pathogen was most unusual in their hospital. Multivariate analysis showed that bacteremia and superinfections with *Acinetobacter* were associated with mortality [21]. Another Spanish cohort of 989 consecutively hospitalized patients found a 3.8% overall incidence of secondary infection in patients with Covid-19, but the proportion of cases was higher among individuals admitted to the ICU with more than half of the events. Gram-negative bacteria were also the most prevalent and 28% of those who developed infection in the ICU had identification of at least one bacterium with a resistant multi-drug profile. Longer hospital stays and higher mortality were observed in those who evolved with healthcare-related infection [22].

A small Chinese cohort study with 36 ICU patients had a prevalence of secondary bacterial infection of 13.9%. The most common agents found in cultures were *Burkholderia cepacia*, *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*, all isolated from tracheal aspirate or bronchoalveolar lavage, showing that exposure to mechanical ventilation preceded the occurrence of infections. In this cohort,

multi drug resistant bacteria were not found [23]. Another Chinese study with 38 severe and critical COVID-19 patients showed a 57.9% prevalence of superinfection, most of which (21/22) were respiratory, with Gram negatives responsible for half of these. No mention of multiressistance was made [24].

In France, a prospective cohort of 54 ICU patients had 49 of their patients on invasive mechanical ventilation. Cultures of bronchoalveolar lavage identified secondary bacterial infection in 37% of inpatients, and of this total, 75% were VAP. This compares to our 29.8% incidence of superinfection, of which 33/57(58%) were VAP. However, their profile of etiologic agents showed a higher prevalence for *Stenotrophomonas maltophilia*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* with 13%, 20% and 33%, respectively, while in our study we had *Acinetobacter, P. aeruginosa* and *K.pneumoniae*, in 28.9%, 22.7% and 14.4% respectively. Patients who developed VAP presented proportionally more ARDS and acute kidney injury and they remained on mechanical ventilation and in the ICU for longer [25]. We found similar risk factors in our study: the group of patients with superinfection presented here experienced moderate to severe ARDS, the need for hemodialysis, mechanical ventilation and vasopressor drugs. They also remained for a longer time on mechanical ventilation in the ICU and had a higher proportion of deaths. Furthermore, a study in Qatar evaluated the impact of MDR Gram- negative infections in patients with severe COVID-19 admitted to ICU. They found a total of 78 cases of MDR-Gram negative infection out of 1231 adults (incidence 4.5 per 1000 ICU days); 98 MDR Gram negative isolates were retrieved within a median of 9 days of admission to ICU. More than one MDR Gram-negative were isolated from 17 (21.8%) patients. The most frequent sample sites were the respiratory tract (74, 75.5%) and blood (18, 18.4%). The most frequently isolated MDR Gram-negatives were *Stenotrophomonas maltophilia* (24, 24.5%), *Klebsiella pneumoniae* (23, 23.5%), and *Enterobacter cloacae* (18, 18.4%); the authors hypothesize one or more outbreaks to account for these. Mechanical ventilation days, but not receipt of corticosteroids or tocilizumab, was independently associated with the isolation of MDR Gram negatives. Surprisingly, there was no association between MDR Gram negative infections and 28-day all-cause mortality [26].

A retrospective cohort of 78 patients in Italy investigated the occurrence of CLABSI in ICU patients with Covid-19. They found a high incidence of events, with a higher prevalence of coagulase negative staphylococci, followed by *Enterococcus faecalis* and *Staphylococcus aureus*. Multivariate analysis showed only the use of anti-inflammatory agents such as tocilizumab or methylprednisolone as an independent association for the occurrence of CLABSI [27]. In our sample, of the 57 patients with secondary infection, 14 were diagnosed with CLABSI, with a predominance of Gram-negative bacteria (Supplement 1).

In our population, the most prevalent gram-negative bacteria with a high profile of antimicrobial resistance were *Klebsiella pneumoniae* and *Acinetobacter baumanii*. The first with 57.1% of the cases with sensitivity to ceftazidime/avibactam only and the second with 96.4% of the isolates with sensitivity to colistin and tigecycline only. VAP was the most common type of infection in both cases. In England, an outbreak of *Klebsiella pneumoniae* infection has been reported in an ICU. Eleven of the 20 cases had a

hostile profile of antimicrobial resistance, which was not reported. The site of infection was the bloodstream and mortality was also not mentioned [28].

In Brazil, multidrug resistant *Acinetobacter* and enterobacteria are prevalent pathogens preceding the COVID-19 pandemic, and VAP is the most frequent ICU-acquired infection [29], as shown in a recent multi-hospital point prevalence study of healthcare-associated infections in 28 adult ICUs. In the European Union, resistance to carbapenems is also worrying and precedes the pandemic, and the impact of COVID-19 on antimicrobial resistance may be deleterious [30]. Other intensive care units dedicated to the care of COVID-19 patients both in the public and private sectors in Rio de Janeiro have CRAB as the main infectious challenge (unpublished data).

The concern with infectious complications related to health care and coping with infections by antibiotic resistant bacteria is one of the most important public health issues of our time. The limited available evidence whether to initiate or not antibiotics for patients in the beginning of the COVID-19 pandemic, the scarcity of evidence on antibiotic choice, the work overload of health professionals and rapid patient deterioration probably resulted in the indiscriminate use of antibiotics and contributed to the spread of multi-drug resistant microorganisms [31, 32].

As limitations, ours is a single center observational study, relying on the quality of medical records. Thus our findings may not be extrapolated to other ICUs.

In conclusion, we found a high incidence of healthcare-related infection in patients with Covid-19 admitted to the ICU, with a higher prevalence of Gram-negative bacteria and a high incidence of multidrug resistance. The most common infection was VAP. The SAPS 3 score was the only factor associated with infections acquired in the ICU. Superinfections of any type and VAP were associated with higher mortality.

Abbreviations

ARDS - acute respiratory distress syndrome

BMI - body mass index

CAUTI - catheter-associated urinary tract infection

CI - confidence intervals

CLABSI - central line-associated bloodstream infections

COPD - chronic obstructive pulmonary disease

Covid-19 - disease caused by the new coronavirus

CRAB - carbapenem resistant *Acinetobacter*

DM - diabetes mellitus

HAP - hospital-acquired pneumonia

ICU - intensive care unit

MDR - multidrug resistance

OR - odds ratio

SAH - systemic arterial hypertension

SAPS 3 - Simplified Acute Physiology Score 3

VAP - ventilator-associated pneumonia

Declarations

Ethical approval and consent to participate

This study was approved by the "Comitê de Ética em Pesquisa da Universidade do Estado do Rio de Janeiro" and the number of the approved opinion was 4,036,509. Informed consent was waived by Comitê de Ética em Pesquisa da Universidade do Estado do Rio de Janeiro due to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

We declare that all data and materials produced by the analyzes of our study are divided between the main manuscript and the document with supplementary/complementary material. For this reason, there is no need to share another repository online. We are at disposal to resolve any doubts regarding the published data.

Competitive interests

The authors declare that they have no competing interest.

Financing

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Rafael Lessa da Costa designed the study, performed the statistical analysis and wrote the main text of the manuscript. Cristiane da Cruz Lamas wrote the main text of the manuscript and participated in the interpretation of the data. Luiz Fernando Nogueira Simvoulidis, participated in the interpretation of the data. Claudia Adelino Espanha participated in data interpretation. Lorena Pinto Monteiro Moreira participated in data acquisition. Renan Alexandre Baptista Bonancim participated in data acquisition. João Victor Lehmkuhl Azeredo Weber participated in data acquisition. Max Rogerio Freitas Ramos participated in the final review. Eduardo Costa de Freitas Silva participated in the final review. Liszt Palmeira de Oliveira participated in the final review. All authors reviewed the manuscript.

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Funding sources

Declarations of interest: none.

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Tables

Table 1. Clinical and laboratory features of 191 adult patients with Covid-19 admitted to ICU stratified according to presence of ICU-acquired superinfection.

	All patients (n = 191)	Patients with superinfection (n = 57)	Patients without superinfection (n = 134)	p-value
Characteristics				
Age (years)	70.5 [58.5 − 80.1]	73.3 [63.6 − 77.5]	56.2 [45.5 − 78.1]	0.9270
Male	116 (60.7%)	38 (66.7%)	78 (58.2%)	0.2730
BMI (Kg/m^2)	32.0 [25.0 − 33.0]	31.0 [26.0 − 35.0]	30.0 [27.0 − 35.0]	0.1240
eGRF (on admission) (mL/min/1,73m²)	67.9 ± 30.0	72.7 ± 31.8	80.0 ± 33.3	0.0540
Δ symptoms-hospitalization (days)due to COVID-19	7.0 [4.0 − 9.0]	6.0 [4.0 − 8.0]	7.0 [5.0 − 8.0]	**0.0310**
SAPS 3	45.0 [29.0 − 71.0]	75.0 [53.0 − 82.0]	48.0 [40.0 − 71.0]	**0.0001**
CRP levels(mg/dL)	10.0 [6.0 − 21.0]	18.0 [7.0 − 26.0]	14.0 [7.0 − 25.0]	**0.0070**
Comorbidities				
Arterial hypertension	122 (63.9%)	39 (68.4%)	83 (61.9%)	0.3940
Diabetes	72 (37.7%)	16 (28.1%)	56 (41.8%)	0.0730
Asthma	8 (4.2%)	1 (1.8%)	7 (5.2%)	0.2730
COPD	14 (7.3%)	2 (3.5%)	12 (9.0%)	0.1860
Coronary disease	22 (11.5%)	7 (12.3%)	15 (11.2%)	0.8300
Ventricular dysfunction	12 (6.2%)	4 (7.1%)	8 (5.9%)	0.3970
Cancer	12 (6.2%)	3 (5.3%)	9 (6.7%)	0.7050
Use of corticosteroids in the ICU	34 (24.3%)	16 (34.8%)	18 (19.1%)	**0.0430**
Complications				
ARDS mild	21 (11.0%)	8 (14.0%)	13 (9.7%)	0.3810
ARDS moderate and severe	98 (51.3%)	47 (82.4%)	51 (38.0%)	**0.0001**

Hemodialysis	55 (28.8%)	33 (57.9%)	22 (16.4%)	**0.0001**
Mechanical ventilation	115 (60.2%)	56 (98.2%)	59 (44.0%)	**0.0001**
Use of vasopressors	109 (57.4%)	56 (98.2%)	53 (39.8%)	**0.0001**
VTE	30 (15.7%)	13 (22.8%)	17 (12.7%)	0.0790
Hospitalization data				
Length of ICU stay(days)	9.5 [3.2 – 26.0]	40.0 [30.0 – 46.0]	17.0 [11.0 – 26.0]	**0.0001**
Duration of mechanical ventilation (days)	13.0 [8.0 – 24.2]	24.0 [11.0 – 29.0]	9.0 [5.0 – 15.0]	**0.0030**
Length of hospital stay (days)	14.5 [9.0 – 32.0]	48.0 [33.0 – 54.0]	24.0 [18.0 – 36.0]	**0.0001**
Death	68 (35.6%)	27 (47.4%)	41 (30.6%)	**0.0270**

ARDS: acute respiratory distress syndrome, BMI: body mass index, COPD: chronic obstructive pulmonary disease, CRP: C-reactive protein, eGRF: estimated glomerular rate filtration, SAPS 3: *Simplified Acute Physiology Score 3*, VTE: venous thromboembolism.

Table 2. Comparison of patients who died and survived in 191 adult patients with Covid-19 admitted to ICU, stratified by type of superinfection.

		Deaths	Survivors	OR	CI 95%	p-value
Total number of patients		(n=68)	(n=123)			
Patients with superinfection	57	27(39.7%)	30 (24.4%)	2.041	1.080 – 3.859	**0.0270**
VAP	33	21 (30.9%)	12 (9.8%)	4.133	1.881 – 9.079	**0.0001**
CLABSI	14	7 (10.3%)	7 (5.7%)	1.902	0.638 – 5.670	0.2430
CAUTI	6	1 (1.5%)	5 (4.1%)	0.215	0.026 – 1.753	0.1160
Tracheobronchitis	15	4 (5.9%)	11 (8.9%)	0.636	0.195 – 2.081	0.4510

CAUTI: catheter-associated urinary tract infection, CLABSI: central line-associated bloodstream infections, VAP: ventilator-associated pneumonia.

Table 3. Etiological agents identified in ICU-acquired superinfections of 57 adult patients admitted due to COVID-19.

Etiological agent	n (%)
Acinetobacter baumannii	28 (28.9%)
A. baumannii multi-drug resistant[¥]	27 (27.8%)
Pseudomonas aeruginosa	22 (22.8%)
P. aeruginosa carbapenemic resistant	4 (4.1%)
P. aeruginosa multi-drug resistant[§]	1 (1.0%)
Klebsiella pneumoniae	14 (14.6%)
K. pneumoniae multi-drug resistant[£]	8 (8.2%)
K. pneumoniae with expanded spectrum to beta-lactamases	3 (3.1%)
K. pneumoniae carbapenem resistant	1 (1.0%)
Staphylococcus aureus	8 (8.2%)
S. aureus methicillin resistant	4 (4.1%)
Enterococcus faecalis	7 (7.2%)
Stenotrophomonas maltophilia	6 (6.2%)
Burkholderia cepacia	2 (2.0%)
Candida sp.	3 (3.1%)
Enterobacteria[¶]	4 (4.0%)
Others[§]	3 (3.0%)
Total	97 (100%)

[¥] sensitive to colistin and tigecycline only , [£] sensitive to ceftazidime/avibactam only, [¶] *Enterobacter aerogenes, Escherichia coli, Enterobacter cloacae,* [§] *Staphylococcus haemolyticus, Chryseobacterium indologenes.*

Table 4. Bivariate analysis of factors related to the outcome of ICU-acquired superinfections in 191 adult patients admitted to ICU due to Covid-19.

	Bivariate		
Variables	OR	CI 95%	p-value
Age (years)	1.001	0.981 − 1.022	0.905
Male	0.696	0.364 − 1.333	0.275
BMI (Kg/m^2)	1.044	0.991 − 1.099	0.104
eGRF	0.990	0.979 − 1.000	0.056
Hypertension	0.751	0.389 − 1.451	0.394
Diabetes	1.840	0.939 − 3.603	0.075
SAPS 3	1.035	1.019 − 1.051	**0.001**
CRP	1.039	1.011 − 1.068	**0.005**
Use of corticosteroids in the ICU	2.252	1.017 − 4.987	**0.045**
ARDS mild	1.520	0.593 − 3.895	0.384
ARDS moderate and severe	7.025	3.335 − 14.801	**0.001**
Hemodialysis	7.000	3.488 − 14.050	**0.001**
Mechanical ventilation	71.186	9.571 − 529.47	**0.001**
Vasopressor drug	84.528	11.35 − 629.36	**0.001**
VTE	2.033	0.913 − 4.530	0.082
Time on mechanical ventilation (days)	1.125	1.028 − 1.231	**0.011**

ARDS: acute respiratory distress syndrome, BMI: body mass index, CRP: C-reactive protein, eGRF: estimated glomerular rate filtration, SAPS 3: *Simplified Acute Physiology Score 3*, VTE: venous thromboembolism.

Supplementary Files

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- Supplement1.docx