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COVID-19 and bacterial superinfections: clinical and microbiological profiles, and determinants of mortality in a reference center in Quito, Ecuador.

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Keywords: sepsis; COVID-19; mortality; antibacterials.

Abstract. The massive prescription of antimicrobials accelerated the generation of multi-resistant bacteria during the SARS-CoV-2 pandemic. This work aims to present the epidemiological, clinical, and microbiological profiles of a series of patients with bacterial superinfections hospitalized in a COVID-19 reference center. We conducted a retrospective observational study in adult COVID-19 patients hospitalized between January and December 2021 who presented with bacterial superinfections. Mortality at discharge was the variable outcome. The median age of the 240 patients included in the study was 55 years, and the male sex predominated at 68.75%. The median stay of hospitalization was 24 days. Superinfections occurred in 55% of patients with mechanical ventilation. The most frequent bacteria were KPC-producing *Klebsiella pneumoniae complex* (24.17%), ESBL-producing *Klebsiella pneumoniae complex* (17.92%), and carbapenem-resistant *Pseudomonas aeruginosa* (13.75%). The most used empirical and targeted antibiotic schemes consisted of the association of carbapenem, glycopeptides, and aminoglycosides (56.09 and 38.55%, respectively). In the multivariate analysis, older age (p= 0.006, OR 1.03, 95% CI: 1.01-1.06), central venous catheter-related bacteremia (CLBSI) (p= 0.028, OR 1.94, 95%CI: 1.07-3.49), and the use of colistin associated with other antibiotics as targeted therapy (p: 0.028, OR 12, 95%CI: 1.30-110.52), were independent predictors of mortality. In this series, we found that in patients with COVID-19 and bacterial superinfection, age, CLBSI, and colistin use were independent predictors of non-survival. The most frequently isolated microorganisms were ESBL- and KPC-producing enterobacterales and non-fermenting Gram-negative bacilli resistant to carbapenems.

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COVID-19 y sobreinfección bacteriana: perfil clínico, microbiológico y determinantes de mortalidad en un centro de referencia en Quito, Ecuador.

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Palabras clave: septicemia; COVID-19; mortalidad; antibacterianos.

Resumen. En la pandemia por SARS-CoV-2, la prescripción masiva de antimicrobianos aceleró la generación de bacterias multirresistentes. El objetivo de este trabajo fue presentar el perfil epidemiológico, clínico y microbiológico de una serie de pacientes con sobreinfección bacteriana, hospitalizados en un centro de referencia COVID-19. Se realizó un estudio observacional retrospectivo, en pacientes adultos hospitalizados entre enero y diciembre de 2021 con COVID-19, que presentaron sobreinfecciones bacterianas. La mortalidad al egreso fue la variable desenlace. En 240 pacientes, la mediana de edad fue 55 años y predominó el sexo masculino 68,75%. La mediana de hospitalización, fue 24 días. El 55% de las sobreinfecciones se presentó en pacientes con ventilación mécanica. Las bacterias más frecuentes, fueron *Klebsiella pneumoniae complex* productora KPC (24,17%), *Klebsiella pneumoniaecomplex* productora ESBL (17,92%) y *Pseudomonas aeruginosa* resistente a carbapenémicos (13,75%). Los esquemas antibióticos empíricos y dirigidos más utilizados constaron de la asociación de carbapenémico, glicopéptido y aminoglucósido (56,09 y 38,55% respectivamante). En el análisis multivariado la mayor edad (p= 0,006 OR 1,03 IC95%: 1,01-1,06); la bacteriemia relacionada a catéter venoso central (CLBSI) (p: 0,028 OR 1,94 IC95%: 1,07-3,49) y el uso de colistina asociado a otros antibióticos como terapia dirigida (p= 0,028 OR 12 IC95%: 1,30-110,52), fueron predictores independientes de mortalidad. En esta serie encontramos que en pacientes con COVID-19 y sobreinfección bacteriana, la edad, la CLBSI y el uso de colistina, fueron predictores independientes de no supervivencia. Los microorganismos más frecuentemente aislados fueron los enterobacterales productores de ESBL y KPC y los bacilos Gram negativos no fermentadores resistentes a carbapenémicos.

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INTRODUCTION

COVID-19 is an emerging viral disease initially reported in Wuhan-China at the end of 2019, rapidly expanding and, in months, collapsed global health systems [1]. Regardless of the speed with which the causative agent, a beta coronavirus, was identified and sequenced and what this meant for developing the first vaccines, compassionate drug use and the abuse of antibiotics were common global scenarios [2,3].

The prescription and self-medication of antimicrobials, many of them for exclusive and restricted hospital use, seeking to reduce the mortality and morbidity associated with this disease, accelerated the selective appearance of multi-resistant bacteria [4].

These bacteria generated significant phenotypic and antibiotype changes in global hospital epidemiology, which propelled a revolution in the massive use of empirical and targeted (directed) antibiotic therapy, using multiple schemes and with unusual antibiotics such as polymyxins and carbapenems on a large scale [5]. In addition, given the high rates of multi-resistance, new broad-spectrum antibiotics were required. However, they were not available in the lists of essential drugs in the public system and were particularly expensive. This kind of antibiotic therapy made the availability of the drugs the exception and not the rule in low-income centers.

With the advent and mass use of vaccines and the use of drugs such as steroids, specific antivirals, and monoclonal antibodies that have demonstrated their efficacy in extensive clinical studies, COVID-19 is on the brink of becoming endemic, and its morbidity and mortality are minor, despite the appearance of more effective variants in its transmission [6].

Falcone *et al*. [7] have reported the results from a nationwide multicenter study in Italy, performed with 1276 patients with bacteremia due to Gram-negative bacilli, in which they observed a marked expansion of resistance to carbapenems and other molecules, new resistance mechanisms, and associated high mortality.

This work aims to present the epidemiological, clinical, and microbiological profiles of a series of patients with bacterial superinfections hospitalized in a center that exclusively treated COVID-19 in Quito, Ecuador.

MATERIALS AND METHODS

Location

The study was performed in a second-level hospital, a regional reference center for COVID-19, located in Quito, Ecuador's capital (2850 meters above sea level), in the province of Pichincha (with a total population of 3,340,039).

Study design

We conducted an analytical retrospective observational study. The universe to be considered consisted of all adult patients hospitalized from January 1, 2021, to December 31, 2021, with a diagnosis of COVID-19. Anonymized data were collected from the consultation database of the Infectologist in charge of infection control and from the electronic clinical records of adult patients admitted to the different areas of the hospital with a diagnosis of COVID-19.

Population and sample size

The universe to be considered consisted of all adult patients hospitalized from January 2021 to December 2021 with a diagnosis of COVID-19. All adult patients diagnosed with healthcare-associated infections (superinfections) were included in the study. A total of 240 patients met the inclusion criteria.

Inclusion criteria

Patients admitted to the health center with a diagnosis of COVID-19 confirmed by rt-PCR and who presented during their hospital stay any healthcare-associated infection (superinfection) determined by the clinical judgment of the treating physician and the infectious disease specialist, whose evaluation was requested. This request was based on findings from the physical examination, laboratory tests, and imaging studies and, with microbiological confirmation, by isolating pathogenic microorganisms in samples taken appropriately.

Exclusion criteria

Patients admitted to our hospital without a confirmed diagnosis of COVID-19 were not included in the study, nor were those who did not present superadded infections during their hospital stay, patients with known coinfections on admission, or transferred with infections acquired in other hospitals. Neither were included those patients with negative microbiological results, whose

cultures were not taken, or whose reports suggested sample contamination.

Data Collection

The clinical and epidemiological variables obtained and analyzed from electronic medical records were age, gender, comorbidity, diagnosis of associated bacterial infections, antibiotic treatment schemes received (empirical and culture-directed), hospital stay, and outcome. Severity indicator biomarkers were also collected: complete blood count and glucose, creatinine, D-dimer, ferritin, lactate dehydrogenase, and C-reactive protein levels.

The information on the cultures taken, the microbiological isolation, and susceptibility profiles were obtained directly from the reports of the Microbiology area of the Hospital's Clinical Laboratory.

Statistical analysis

The analyses were performed with the IBM SPSS version 23 statistical package. Descriptive statistics was used, employing tables and graphs, representing the qualitative variables in absolute and relative values, whereas measures of central tendencies and variabilities were used for the quantitative variables.

In inferential statistics, bivariate analyses were performed to determine the variables to be considered in the multivariate analysis. With this purpose, the Chi-square test or Fisher's exact statistic were applied for the qualitative variables, while for the quantitative ones, the Mann-Whitney test was used when data did not comply with normality. Multivariate logistic regression analysis was used to relate the variables with mortality. Statistical significance was established as $p<0.05$.

RESULTS

Two hundred forty patients with a median age of 55 and a predominance of men (68.75%) were analyzed. The median hospital stay was 24 days. When comparing age by the discharge condition, significant differences were observed with $p= 0.002$, with medians of 52.5 years in survivors vs. 58.5 years in non-survivors. The hospital stay presented significant differences by discharge condition with $p<0.001$, with the median stay being 29 days in survivors vs. 16 days in non-survivors (Table 1).

Table 2 reports the analytical and cytometric values, which indicate that although the elevation of biomarkers characteristic of severe forms of the disease is striking, such as the white count, C-reactive protein, D-dimer, and ferritin, there were no significant differences when compared to the condition at discharge.

Regarding associated infections, ventilator-associated pneumonia (VAP) was observed more frequently in 55% of cases,

Table 1
Relationship between clinical characteristics and discharge condition.

Clinical Characteristics	Total	Discharge Condition		p
		Survivor	Non-survivor	
Age (median (IQR))*	55 (45-64)	52.5 (42.75-62)	58.5 (48.75-67.25)	0.002
Sex (n (%))**				
Female	75 (31.25)	45 (30.82)	30 (31.91)	0.858
Male	165 (68.75)	101 (69.18)	64 (68.09)	
Days of stay (median (IQR))*	24 (16-35)	29 (21-41.5)	16 (12-22.5)	<0.001

* Mann-Whitney test, ** Chi-square test.

Table 2
Relationship between analytical parameters and cytometry by discharge condition.

Cytometry and Analytical Parameters	Total	Discharge Condition		p
		Survivor	Non-Survivor	
	Median (IQR)	Median (IQR)	Median (IQR)	
Leukocytes (cells x mm^3)	11510 (8210-14770)	11940 (8120-14910)	10710 (8400-14590)	0.6531
Neutrophils (cells x mm^3)	9640 (6840-13320)	9920 (6620-13190)	9100 (7200-13340)	0.8527
Lymphocytes (cells x mm^3)	750 (520-1130)	760 (540-1160)	710 (470-1030)	0.2554
NLR (Neutr-Lymph ratio)	12.85 (7.46-21.09)	13.11 (7.13-20.52)	12.36 (7.48-22.4)	0.6191
Neutrophils (%)	88 (82-91)	88 (81-91)	88 (83-92)	0.4382
Lymphocytes (%)	7 (4-11)	7 (4-11)	7 (4-11)	0.6428
Hemoglobin (g/dL)	15.5 (14.2-17)	15.55 (14.1-17)	15.45 (14.3-17.2)	0.8504
Hematocrit (%)	46 (42-50)	47 (42-51)	0.46 (42-50)	0.5625
Platelets (cells x mm^3)	253500 (204250-331750)	271000 (206750-342500)	238500 (198500-312750)	0.0732
MPV (fL)	8.8 (8.3-9.6)	8.7 (8.3-9.55)	8.9 (8.3-9.63)	0.4118
Glucose (mg/dL)	134 (107-168)	133 (106-171.2)	137 (109-164.25)	0.6469
Creatinine (mg/dL)	0.87 (0.68-1.09)	0.86 (0.66-1.08)	0.89 (0.75-1.09)	0.3726
D Dímer (ng/mL)	1027.25 (653.28-1741.28)	1100.6 (653.4-1860.1)	972.5 (640.3-1672.1)	0.4093
Ferritin (ng/mL)	1087.2 (604.6-1639.7)	1026.7 (595.98-1649.75)	1111 (649.25-1543.55)	0.6414
LDH (UI/L)	855 (627-1045.75)	838 (627-1078)	864 (629-982)	0.5934
PCR (mg/dL)	15.39 (9.19-23.25)	16.42 (8.3-24.37)	14.67 (10.23-21.22)	0.7600

Mann-Whitney test.

followed by catheter-associated urinary infections (CAUTI) at 43.75%, central line-associated bloodstream infection (CLBSI) 31. 25%, and colonization at 15.42%, among others. The CLBSI presented significant differences by discharge condition with a p of 0.030; the proportions were 26.03% in survivors vs. 39.36% in non-survivors (Table 3).

Among the most frequent bacteria causing superadded infections in our study, KPC-type carbapenem-producing Klebsiella pneumoniae complex was observed in 24.17% of the cases, followed by Klebsiella pneumoniae producing extended-spectrum β-lactamase (ESBL) in 17.92%, and carbapenem-resistant Pseudomonas aeruginosa in 13.75%, among others. Serratia marcescens presented significant differences by discharge condition with a p of 0.013, the proportion of this bacterium being 6.16% in survivors vs. 0% in non-survivors (Table 4).

Among the most used antibiotic schemes, meropenem + vancomycin + amikacin was observed in 56.09% of the empirical scheme and 38.55% of directed schemes. In the directed scheme, significant differences were observed by discharge condition with a p = 0.036, specifically for colistin + others, whose proportions were 16.95% in survivors vs. 41.67% in non-survivors (Table 5).

Multivariate logistic regression analysis was performed to determine the relationship between age, CLBSI, and antibiotic scheme with mortality, observing the following: age was related to mortality with p = 0.006, whereas due to the one-year increase in patients, the risk of mortality of patients was increased by 3%.

Table 3
Relationship between associated infections and discharge condition.

Associated Infections	Total	Discharge Condition		p
		Survivor	Non-Survivor	
	n (%)	n (%)	n (%)	
VAP	132 (55)	80 (54,79)	52 (55,32)	0,936
CAUTI	105 (43,75)	68 (46,58)	37 (39,36)	0,272
CLBSI	75 (31,25)	38 (26,03)	37 (39,36)	0,030*
Colonization	37 (15,42)	27 (18,49)	10 (10,64)	0,100
SSTI	5 (2,08)	2 (1,37)	3 (3,19)	0,383
SSI	5 (2,08)	4 (2,74)	1 (1,06)	0,651
ENT	1 (0,42)	1 (0,68)	0 (0)	1,000

* significant difference, Chi-square test or Fisher's exact test. VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary infections; CLBSI: central line-associated bloodstream infection; SSTI: skin and soft tissue infections; SSI: surgical site infection; ENT: ear, nose, and throat infections (otitis, retro tonsillar abscesses, etc.).

Table 4
Relationship between the type of bacteria and discharge condition.

Bacteria	Total	Discharge Condition		p
		Survivor	Non-Survivor	
	n (%)	n (%)	n (%)	
E. coli	32 (13.33)	21 (14.38)	11 (11.7)	0.698
E. coli ESBLs	24 (10)	17 (11.64)	7 (7.45)	0.290
Enterobacter cloacae complex	5 (2.08)	3 (2.05)	2 (2.13)	1.000
Enterococcus faecalis	9 (3.75)	5 (3.42)	4 (4.26)	0.740
K. oxytoca	5 (2.08)	3 (2.05)	2 (2.13)	1.000
K. oxytoca ESBLs	5 (2.08)	4 (2.74)	1 (1.06)	0.651
K. pneumoniae complex	14 (5.83)	10 (6.85)	4 (4.26)	0.403
K. pneumoniae complex ESBLs	43 (17.92)	22 (15.07)	21 (22.34)	0.152
K. pneumoniae complex KPC	58 (24.17)	40 (27.4)	18 (19.15)	0.145
Morganella morganii	6 (2.5)	3 (2.05)	3 (3.19)	0.681
Proteus mirabilis	5 (2.1)	2 (1.4)	3 (3.2)	0.383
Proteus mirabilis ESBLs	7 (2.92)	3 (2.05)	4 (4.26)	0.437
P. aeruginosa	19 (7.92)	11 (7.53)	8 (8.51)	0.784
P. aeruginosa CR	33 (13.75)	18 (12.33)	15 (15.96)	0.426
Serratia marcescens	9 (3.75)	9 (6.16)	0 (0)	0.013*
S. aureus complex	19 (7.92)	12 (8.22)	7 (7.45)	1.000
S. aureus complex MR	11 (4.58)	5 (3.42)	6 (6.38)	0.348
S. epidermidis	17 (7.08)	8 (5.48)	9 (9.57)	0.303
S. hominis MR	6 (2.5)	4 (2.74)	2 (2.13)	1.000
Streptococcus pneumoniae	5 (2.16)	4 (2.86)	1 (1.1)	0.651

*significant difference, Chi-square test or Fisher's exact test. ESBLs: extended-spectrum beta-lactamase; KPC: KPC-type carbapenemase; MR: methicillin-resistant; CR: carbapenemase-resistant.

Table 5
Relationship between antibiotic scheme and discharge condition.

Antibiotic Scheme	Total	Discharge Condition		p
		Survivor	Non-survivor	
	n (%)	n (%)	n (%)	
Empirical				
Aminopenicillin + others	41 (17,83)	29 (20,57)	12 (13,48)	0,151
Colistin + others	28 (12,17)	21 (14,89)	7 (7,87)	
Meropenem + vancomycin + Amikacin	129 (56,09)	73 (51,77)	56 (62,92)	
Piperacillin/tazobactam + others	32 (13,91)	18 (12,77)	14 (15,73)	
Directed				
Aminopenicillin + others	13 (15,66)	12 (20,34)	1 (4,17)	0,036*
Colistin + others	20 (24,1)	10 (16,95)a	10 (41,67)b	
Meropenem + vancomycin + Amikacin	32 (38,55)	22 (37,29)	10 (41,67)	
Piperacillin/tazobactam + others	18 (21,69)	15 (25,42)	3 (12,5)	

*significant difference; different superscripts indicate antibiotics that differ by discharge condition, Chi-square test.

CLBSI infections were related to mortality with a p of 0.028, whereas patients with CLBSI infections were 1.94 times more likely not to survive (Table 6).

Among the directed (targeted) antibiotic schemes, it was observed that Colistin + others were related to mortality with a p = 0.028, where patients treated with these antibiotics presented a 12 times greater probability of not surviving compared to those who received aminopenicillins + others (Table 7).

The enzymatic resistance of these bacteria was studied. 40% of the *K. pneumoniae complex* and *E. coli* isolates were ESBL producers. In addition, one out of every five *K. pneumoniae complex* isolates was a KPC producer. The resistance observed to carbapenems by P. aeruginosa is very high: resistance to carbapenems was found in seven out of ten isolates. *S. aureus complex* and *S. epidermidis* showed 30 and 80% resistance to methicillin, respectively (Table 8).

DISCUSSION

This study, conducted on 240 hospitalized patients with COVID-19 who presented with bacterial superinfection, has shown that older male patients with bacteremia who received treatment with antibiotic regimens containing colistin were associated with lower survival.

Of these factors, age, bloodstream infection, and colistin use were independent factors for mortality when adjusted in a multivariate model. Furthermore, it was also observed that VAP was the most frequent site of superinfection; and that enzymatic resistance due to ESBL and KPC-type serine betalactamases was frequent in enterobacteria. The most used empirical scheme was composed of carbapenems, aminoglycosides, and glycopeptides (meropenem, amikacin, and vancomycin), and the presence of carbapenem-resistant P. aeruginosa was relevant.

Patients with severe COVID-19 admitted to a hospital are at greater risk of developing infections during their hospital stay [8–11,] and this risk increases as their hospital stay is prolonged [12]. This increased risk of superinfection is due to greater exposure of patients to immunosuppressive treatments (especially steroids) and also for reasons specific to health centers, of a structural

Table 6
Multivariate analysis for mortality based on age, CLBSI, and empirical antibiotic scheme.

Variables	B	p	OR	OR (95% CI)	
				Lower	Upper
AGE	0.03	0.006*	1.03**	1.01	1.06
CLBSI	0.66	0.028*	1.94**	1.07	3.49
Aminopenicillin + others (reference)					
Colistin + others	-0.15	0.797	0.86	0.28	2.68
Meropenem + Vancomycin + Amikacin	0.59	0.136	1.81	0.83	3.94
Piperacillin/tazobactam + others	0.55	0.278	1.74	0.64	4.71

Note: *significant variables, **factor associated with mortality, based on logistic regression: OR (95% CI): Odds ratio (95% Confidence interval). CLBSI: central venous catheter-related bacteremia.

Table 7
Multivariate analysis for mortality based on a culture-directed antibiotic regimen.

Directed Scheme	B	p	OR	OR (95% CI)	
				Li	LS
Aminopenicillin + others (reference)				1.3	
Colistin + others	2.48	0.028*	12**	0	110.52
Meropenem + Vancomycin + Amikacin	1.70	0.126	5.45	0.62	47.90
Piperacillin/tazobactam + others	0.88	0.472	2.40	0.22	26.12

Note: *significant variable, ** mortality associated factor, based on logistic regression. OR (95% CI): Odds ratio (95% Confidence interval).

type (opening of new ICU beds in other areas of the hospital), organizational (hiring or transferring personnel without prior training in the management of critical patients) and functional (changes in patient care standards, and prolonged use of personal protective equipment). In addition, these patients require vascular access, urinary devices, and invasive mechanical ventilation due to their condition, increasing the risk of infections. These hospital infections are more complex than usual because they are associated with bacteria with resistance to antibiotics[13].

The documented evidence demonstrates that male patients with COVID-19 are at greater risk of presenting more severe forms of COVID-19, with prolonged hospitalizations and more extended use of invasive devices, which increases the risk of superinfection,[5] according to the findings of our study. The mean age in the sample was 55 years, with age ranges between 50 and 60 years, similar to the data reported by other authors [5,10,14]. In addition, this data was associated with higher mortality: the increase in one year of age increases mortality risk by 3%, agreeing with what has been reported in the literature [5,7,10].

The average hospital stay was 24 days, less in the non-survivor group, with a statistically significant difference. As a possible hypothesis, it is proposed that they were patients with more severe diseases that coursed with more torpid and abrupt evolutions, con-

Table 8
Isolated bacteria and enzymatic resistance.

Bacterial species	Enzyme production	%
Klebsiella pneumoniae complex	ESBL/KPC	39.10%/ 20.96%
Pseudomonas aeruginosa	CR	70.42%
Escherichia coli	ESBL	40.57%
Staphylococcus aureus complex	MRSA	31.11%
Staphylococcus epidermidis	MR	81.25%
Proteus mirabilis	ESBL	68.75%
Enterobacter aerogenes	AmpC	10.00%
Klebsiella oxytoca	ESBL/ KPC	12.50%/ 12.50%
Enterobacter cloacae complex	ESBL	16.60%

ESBL: extended-spectrum beta-lactamase, KPC: KPC-type carbapenemase, MR: methicillin-resistant, CR: carbapenemase-resistant.

sistent with what has been reported by some authors [10,12,15,16].

The laboratory data (Table 2) show that the two groups (survivors and deceased) generally presented similar patterns of acute inflammatory reaction, state of hyperinflammation, and hypercoagulability, with no statistically significant differences. It is suggested that both groups were patients admitted with severe disease with systemic involvement. From the point of view of the severity of the condition caused by COVID-19, they were similar groups.

VAP was the most common infection reported in this investigation, representing 55% of infections. In other studies, it has been reported that VAP represented between 40% and 60% of documented superinfections in patients with COVID-19. The highest predisposition to these processes has been associated with prolonged ventilation, prone position, use of corticosteroids, lung damage, and episodes of cross-contamination, most likely due to the prolonged use of personal protective equipment. In addition, the same COVID-19 infection can cause inflammation of the pulmonary vascular endothelium and subsequent thrombosis, creating an environment conducive to bacterial growth [17–19].

The incidence of CLBSI tripled during the pandemic [20]. In this study, patients with this type of infection were 1.94 times more likely not to survive. Other authors have reported higher mortality from CLBSI in patients with COVID-19 (between 40 and 54%) than from this type of infection in pre-pandemic or non-COVID-19 patients (between 24 and 33%) [20–22]. This higher mortality may be due to the use of these devices for a longer time, the prone position that limited the care of the line, and the breach of asepsis and antisepsis when manipulating the catheter in the harsh conditions faced during the health emergency, generating bacteremia more frequently with a more significant inoculum.

K. pneumoniae complex was the most frequently recovered bacterium in cultures, followed by *P. aeruginosa* and *E. coli*. Generally, the reports in the literature vary widely because of local microbiology. However, most of the studies at a global and regional level, carried out during the pandemic, agree with this research, showing that these bacteria are the most frequent [5,8,15-17,23].

In our study series, a high percentage of Enterobacterales were ESBL producers, and one in five *K. pneumoniae complex* isolates were KPC-type carbapenemase producers, consistent with other reports in Latin America during the pandemic [24]. Most recovered *Pseudomonas* cultures reported resistance to carbapenems (70%). These findings are worrying due to the impact on public health and the limitation of the therapeutic arsenal against such microorganisms, especially in countries such as Ecuador [25].

In non-randomized clinical studies, using colistin as monotherapy or combination therapy has mixed results; however, it presents higher mortality in patients who previ-

ously received carbapenems [26–28]. In the IDSA guidelines, the use of colistin as targeted therapy is discouraged, giving preference to monotherapy with new antibiotics such as ceftazidime-avibactam [29]. Patients who received colistin (combined with other antibiotics) were associated with higher mortality in our series. We attributed this finding to prior treatment with carbapenems and subsequent resistance to them, the side effects of colistin and associated antibiotics, and the fact that they presented a more severe disease. Moreover, this higher mortality could occur because colistin was indicated as a desperate measure since there were no better therapeutic options available in the hospital or because its susceptibility to the microorganism could not be confirmed since the sensitivity cut-off points had not been established with an antibiogram for the said antibiotic, against certain bacteria and/or in some tissues.

On the other hand, it should be considered that the hospital in this study is located almost 3000 meters above sea level. Although the effect of high altitude (≥1500m) and its potential association with mortality from COVID-19 is still controversial, there are studies in this direction[30,31]; therefore, more research is required in this regard and its impact on the high mortality of severely ill patients with bacterial superinfections.

This work has significant limitations. It is monocentric and retrospective, with the biases inherent in this design; furthermore, there was no control group. There could also be a possible underdiagnosis of fungal infections, which were not reported in this series and constitute a clinical challenge, especially in the context of patients infected with SARS-CoV-2. Finally, the health center needed molecular biology studies to determine resistance genes. Nevertheless, in the case of the *K. pneumoniae complex* isolates, in those cases where the automated system reported strains probably producing KPC, lateral flow tests were carried out, and the strains were sent to the national reference laboratory in Ecuador: Instituto Nacional de Investigación en Salud Pública "Dr. Leopoldo Izquieta Pérez" (INSPI). Molecular biology studies were performed at the institution for confirmation, and the hospital was notified.

In the present retrospective study, we found that in patients with COVID-19 and bacterial superinfection, age, central venous catheter-associated bacteremia, and colistin use were independent predictors of mortality. The most frequently isolated microorganisms were ESBL- and KPC-producing Enterobacterales and non-fermenting Gram-negative bacilli resistant to carbapenems.

These findings are consistent with what has been reported in world and regional series and emphasize the urgent need to establish programs for the rational use of antibiotics, especially in countries with a limited therapeutic arsenal.

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Conflict of interest

There is no conflict of interest.

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JEDD: lead author, conception/design, data collection and analysis, manuscript preparation, and revision. RSM and WCBP: data collection and analysis, literature review. SAM data collection and analysis, preparation, and manuscript revision. JLVP: conception/design, statistical analysis, preparation, and manuscript review. All authors have read and approved submitting the final manuscript to the journal.

REFERENCES

1. **Coronavirus disease (COVID-19) pandemic** [Internet]. [citado 26 de febrero de 2023]. Disponible en: https://www.who.int/europe/emergencies/situations/covid-19
2. **Gong W, Parkkila S, Wu X, Aspatwar A**. SARS-CoV-2 variants and COVID-19 vaccines: Current challenges and future strategies. Int Rev Immunol 2022;28:1-22.
3. **Pérez-Martínez CA, Padilla-Santamaría F, Helguera-León SA, Mejía-Cornejo JJ, Casados-Rodríguez BE, Martínez-Abarca CI, Zamarrón-López ÉI, Pérez-Nieto OR.** Antimicrobial use and abuse in COVID-19: When is its use justified? Med Int Mex 2021;37(6):1015-1029.
4. **Hu S, You Y, Zhang S, Tang J, Chen C, Wen W, Wang C, Cheng Y, Zhou M, Feng Z, Tan T, Qi G, Wang M, Liu X**. Multidrug-resistant infection in COVID-19 patients: A meta-analysis. J Infect 2023;86(1):66-117.
5. **Nebreda-Mayoral T, Miguel-Gómez MA, March-Rosselló GA, Puente-Fuertes L, Cantón-Benito E, Martínez-García AM, Muñoz-Martín AB, Orduña-Domingo A.** Infección bacteriana/fúngica en pacientes con COVID-19 ingresados en un hospital de tercer nivel de Castilla y León, España. Enferm Infecc Microbiol Clin 2022;40(4):158-165.
6. **Murakami N, Hayden R, Hills T, Al-Samkari H, Casey J, Del Sorbo L, Lawler P, Sise M, Leaf D.** Therapeutic advances in COVID-19. Nat Rev Nephrol 2023;19(1):38-52.
7. **Falcone M, Tiseo G, Carbonara S, Marino A, Di Caprio G, Carretta A, Mularoni A, Mariani M, Maraolo A, Scotto R, Dalfino L , Corbo L, Macera M, Medaglia A, d'Errico M, Gioè C, Sgroi C, Del Vecchio R, Ceccarelli G, Albanese A, Buscemi C, Talamanca S, Raponi G, Foti G, De Stefano G, Franco A, Iacobello C, Corrao S, Morana U, Pieralli F, Gentile I, Santantonio T, Cascio A, Coppola N, Cacopardo B, Farcomeni A, Venditti M, Menichetti F**. Mortality attributable to bloodstream infections caused by different carbapenem-resistant Gram-negative bacilli: results from a nationwide study in Italy (ALARICO Network). Clin Infect Dis 2023;ciad100. Disponible en: *https://doi.org/10.1093/cid/ciad100*
8. **Marin-Corral J, Pascual-Guardia S, Muñoz-Bermúdez R, Salazar-Degracia A, Climent C, Vilà-Vilardell C, Acer M, Picornell M, Restrepo MI, Masclans JR,** Álvarez-**Lerma F.** Health care-associated infections in patients with COVID-19 pneumonia in COVID critical care areas. Med Intensiva 2022;46(4):221-223.
9. **Buetti N, Ruckly S, de Montmollin E, Reignier J, Terzi N, Cohen Y, Siami S, Dupuis C, Timsit JF.** COVID-19 increased the risk of ICU-acquired bloodstream infections: a case-cohort study from the multicentric OUTCOMEREA network. Intensive Care Med 2021;47(2):180-187.
10. **Soriano MC, Vaquero C, Ortiz-Fernández A, Caballero A, Blandino-Ortiz A, de Pablo R.** Low incidence of co-infection, but high incidence of ICU-acquired infections in critically ill patients with COVID-19. J Infect. 2021;82(2):e20-1.
11. **Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Bordell A, Adalia R, Zattera L, Ramasco F, Monedero P, Maseda E, Martínez A, Tamayo G, Mercadal J, Muñoz G, Jacas A, Ángeles G, Castro P, Hernández-Tejero M, Fernandez J, Gómez-Rojo M, Candela Á, Ripollés J, Nieto A, Bassas E, Deiros C, Margarit A, Redondo FJ, Martín A, García N, Casas P, Morcillo C, Hernández-Sanz ML.** Patient characteristics, clinical course and factors

associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: A prospective, cohort, multicentre study. Rev Esp Anestesiol Reanim (Engl Ed) 2020;67(8):425-437.

12. **Vaughn VM, Gandhi TN, Petty LA, Patel PK, Prescott HC, Malani AN, Ratz D, McLaughlin E, Chopra V, Flanders SA.** Empiric antibacterial therapy and community-onset bacterial coinfection in patients hospitalized with Coronavirus Disease 2019 (COVID-19): A multi-hospital cohort study. Clin Infect Dis 2021;72(10):533-541.
13. **Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, Soucy JR, Daneman N.** Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect 2020;26(12):1622-1629.
14. **Varshini M K, Ganesan V, Charles J.** Secondary bacterial and fungal infections in COVID-19 patients. Int J Antimicrob Agents. 2021;58:21003526.
15. **Westblade LF, Simon MS, Satlin MJ**. Bacterial Coinfections in Coronavirus Disease 2019. Trends Microbiol 2021;29(10):930-941.
16. **Lucien MAB, Canarie MF, Kilgore PE, Jean-Denis G, Fénélon N, Pierre M, Cerpa M, Joseph GA, Maki G, Zervos MJ, Dely P, Boncy J, Sati H, Rio AD, Ramon-Pardo P**. Antibiotics and antimicrobial resistance in the COVID-19 era: perspective from resource-limited settings. Int J Infect Dis 2021;104:250-254.
17. **Ippolito M, Misseri G, Catalisano G, Marino C, Ingoglia G, Alessi M, Consiglio E, Gregoretti C, Giarratano A, Cortegiani A**. Ventilator-associated pneumonia in patients with COVID-19: a systematic review and meta-analysis. Antibiotics (Basel) 2021;10(5):545.
18. **Rouyer M, Strazzulla A, Youbong T, Tarteret P, Pitsch A, de Pontfarcy A, Cassard B, Vignier N, Pourcine F, Jochmans S, Monchi M, Diamantis S**. Ventilator-associated pneumonia in COVID-19 patients: a retrospective cohort study. Antibiotics (Basel) 2021;10(8):988.
19. **Boyd S, Nseir S, Rodriguez A, Martin-Loeches I.** Ventilator-associated pneumonia in critically ill patients with COVID-19 infection: a narrative review. ERJ Open Research [Internet]. 2022 [citado 26 de febrero de 2023];8(3). Disponible en: https://openres.ersjournals.com/content/8/3/00046-2022
20. **Fakih MG, Bufalino A, Sturm L, Huang RH, Ottenbacher A, Saake K, Winegar A, Fogel R, Cacchione J.** Coronavirus disease 2019 (COVID-19) pandemic, central-line-associated bloodstream infection (CLABSI), and catheter-associated urinary tract infection (CAUTI): The urgent need to refocus on hardwiring prevention efforts. Infect Control Hosp Epidemiol 2022;43(1):26-31.
21. **LeRose J, Sandhu A, Polistico J, Ellsworth J, Cranis M, Jabbo L, Cullen L, Moshos J, Samavati L, Chopra T**. The impact of coronavirus disease 2019 (COVID-19) response on central-line–associated bloodstream infections and blood culture contamination rates at a tertiary-care center in the Greater Detroit area. Infect Control Hosp Epidemiol 2021; 42 (8):997-1000.
22. **Pérez-Granda MJ, Carrillo CS, Rabadán PM, Valerio M, Olmedo M, Muñoz P, Bouza E.** Increase in the frequency of catheter-related bloodstream infections during the COVID-19 pandemic: a plea for control. J Hosp Infect 2022;119:149-154.
23. **Intra J, Sarto C, Beck E, Tiberti N, Leoni V, Brambilla P**. Bacterial and fungal colonization of the respiratory tract in COVID-19 patients should not be neglected. Am J Infect Control 2020;48(9):1130-1131.
24. **Thomas GR, Corso A, Pasterán F, Shal J, Sosa A, Pillonetto M, de Souza Peral RT, Hormazábal JC, Araya P, Saavedra SY, Ovalle MV, Jiménez Pearson MA, Chacón GC, Carbon E, Mazariegos Herrera CJ, Velásquez SDCG, Satan-Salazar C, Villavicencio F, Touchet NM, Busignani S, Mayta-Barrios M, Ramírez-Illescas J, Vega ML, Mogdasy C, Rosas V, Salgado N, Quiroz R, El-Omeiri N, Galas MF, Ramón-Pardo P, Melano RG.** Increased detection

of carbapenemase-producing Enterobacterales bacteria in Latin America and the Caribbean during the COVID-19 pandemic. Emerg Infect Dis 2022;28(11):1-8.

25. **Mendelson M.** BSAC Vanguard Series: Inequality and antibiotic resistance. J Antimicrob Chemother 2022;77(2):277-278.
26. **da Silva KE, Baker S, Croda J, Nguyen TNT, Boinett CJ, Barbosa LS, Tetila A, Simionatto S.** Risk factors for polymyxin-resistant carbapenemase-producing Enterobacteriaceae in critically ill patients: An epidemiological and clinical study. Int J Antimicrob Agents. 2020;55(3):105882.
27. **Yahav D, Farbman L, Leibovici L, Paul M.** Colistin: new lessons on an old antibiotic. Clin Microbiol Infect 2012;18(1):18-29.
28. **Kaye KS, Marchaim D, Thamlikitkul V, Carmeli Y, Chiu CH, Daikos G, Dhar, S, Durante-Mangoni E, Gikas A, Kotanidou A, Paul M, Roilides E, Rybak M, Samarkos M, Sims M, Tancheva D, Tsiodras S, Kett , Patel G, Calfee D, Leibovici L, Power L, Munoz-Price S, Stevenson K, Susick L, Latack K, Daniel J, Chiou C, Divine G, Ghazyaran V, Pogue J.** Colistin monotherapy versus combination therapy for carbapenem-resistant organisms. NEJM Evidence. 2022;2(1):EVIDoa2200131.
29. **IDSA Practice Guidelines** [Internet]. [citado 26 de febrero de 2023]. Disponible en: https://www.idsociety.org/practice-guideline/practice-guidelines/
30. **Rodriguez Lima DR, Pinzón Rondón ÁM, Rubio Ramos C, Pinilla Rojas DI, Niño Orrego MJ, Díaz Quiroz MA, Molano-González N, Ceballos Quintero JE, Arroyo Santos AF, Ruiz Sternberg ÁM.** Clinical characteristics and mortality associated with COVID-19 at high altitude: a cohort of 5161 patients in Bogotá, Colombia. Int J Emerg Med 2022;15(1):22.
31. **Jibaja M, Roldan-Vasquez E, Rello J, Shen H, Maldonado N, Grunauer M, Díaz AM, García F, Ramírez V, Sánchez H, Barberán JL, Paredes JP, Cevallos M, Montenegro F, Puertas S, Briones K, Martínez M, Vélez-Páez J, Montalvo-Villagómez M, Herrera L, Garrido S, Sisa I.** Effect of high altitude on the survival of COVID-19 patients in Intensive Care Unit: a cohort study. J Intensive Care Med 2022;8850666221099827.