Clinical, epidemiological, and laboratory profiles of bacterial infection or colonization among patients hospitalized in COVID-19 and non-COVID-19 intensive care units (ICUs) in Southeast Pará

Perfis clínico, epidemiológico e laboratorial de infecção ou colonização bacteriana em pacientes internados em unidades de terapia intensiva (UTIs) COVID-19 e não COVID-19 no sudeste do Pará

Edlainny Araujo Ribeiro[1], Mateus Pereira Mundoca[1], Mateus Taborda Cachoeira[1], Luana Lopes Nobre[1], Marcia Juciele da Rocha[2]

ABSTRACT

Objectives: To compare the clinical, epidemiological, and laboratory profiles of bacterial infection or colonization among patients hospitalized in COVID-19 and non-COVID-19 intensive care units (ICUs) in Southeast Pará, Brazil. **Methods:** This was a retrospective analytical study based on the analyses of electronic medical records and microbiological reports of patients admitted to the ICU of a regional hospital located in Pará in the Brazilian Amazon due to complications associated with COVID-19 and other causes from March 2020 to December 2021. The sample consisted of data from the medical records of 343 patients collected after approval by the ethics and research committee (opinion number 5281433) was granted. The data extracted from the bacteriological and antibiogram culture reports were analyzed to characterize the clinical-epidemiological profile of the patients. The data were transferred and tabulated in Microsoft Excel 2019 to conduct a descriptive analysis, and the associated statistical analyses were performed using Stata 17.0 statistical software. **Results:** Of the total patients, 59.5% were hospitalized in the COVID-19 ICU and 40.5% were hospitalized in the non-COVID-19 ICU. Most individuals admitted to the COVID-19 ICU and non-COVID-19 ICU were aged between 66 and 78 years and between 54 and 66 years, respectively. The hospitalization duration in the COVID-19 ICU was fewer than 15 days, whereas that in the non-COVID-19 ICU was 15 to 30 days. Deaths were more frequent in the Covid-19 ICU compared to the non-Covid-19 ICU (64% versus 41%). In contrast, hospital discharge was more frequent in the non-Covid-19 ICU (58.3% versus 34.8%).The most prevalent comorbidity in both ICUs was circulatory system disease. Gram-negative bacteria were the most frequent etiological agent in both groups and were present in 63.1% of the cultures analyzed. Regarding the phenotypic profile of resistance, carbapenemase production was detected in 43.0% of the cultures analyzed. Multidrug resistance against antimicrobial drugs was more frequent in the non-COVID-19 ICU (55.7%). Most of the antimicrobial drug prescriptions for were empirical. **Conclusions:** The recurrence of secondary infections and bacterial colonization in both COVID-19 and non-COVID-19 ICU patients should not be underestimated. The clinical, microbiological, and bacterial resistance profiles elucidated in this study highlight the need to develop and implement holistic and assertive strategies to control and mitigate these problems. Which will contribute to an improved prognosis for patients and quality of life patients.

Keywords: COVID-19, Coinfection, Multidrug resistance, Evidence-based medicine, Intensive care units.

RESUMO

Objetivos: Comparar o perfil clínico, epidemiológico e laboratorial das infecções ou colonizações bacterianas entre pacientes internados em UTI COVID-19 e não-COVID-19 no Sudeste do Pará, Brasil. **Métodos:** Trata-se de um estudo analítico retrospectivo baseado na análise de prontuários eletrônicos e laudos microbiológicos de pacientes internados em um hospital regional localizado no Pará, na Amazônia brasileira, devido a complicações associadas à COVID-19 e outras causas no período de março de 2020 a dezembro de 2021. A amostra foi constituída por dados dos prontuários de 343 pacientes coletados após aprovação pelo Comitê de ética em Pesquisa (parecer número 5281433). Os dados extraídos dos laudos de cultura bacteriológica e antibiograma foram analisados para caracterizar o perfil clínico-epidemiológico dos pacientes. Foram realizadas análises descritivas e inferenciais utilizando o Stata 17.0 statistical software. **Resultados:** Do total de

[1] Higher Education College of the Reunited Amazon. Medicine School, Redenção, (PA), Brazil.
[2] Federal University of Pelotas. Postgraduate Program in Biochemistry and Bioprospecting, Pelotas, (RS), Brazil.

https://doi.org/10.11606/issn.2176-7262.rmrp.2023.204460

pacientes, 59,5% estavam internados na UTI COVID-19 e 40,5% na UTI não-COVID-19. A maioria dos indivíduos apresentavam idades entre 54 e 78. O tempo de internação na UTI COVID-19 foi inferior a 15 dias, enquanto na UTI não-COVID-19 foi de 15 a 30 dias. Os óbitos foram mais frequentes na UTI Covid-19 em relação à UTI não-Covid-19 (64% *versus* 41%). Em contrapartida, a alta hospitalar foi mais frequente na UTI não Covid-19 (58,3% *versus* 34,8%). A comorbidade mais prevalente em ambas as UTIs foi a doença do aparelho circulatório. As bactérias Gram-negativas foram os agentes etiológicos mais frequentes em ambos os grupos e estiveram presentes em 63,1% das culturas analisadas. Em relação ao perfil fenotípico de resistência, a produção de carbapenemase foi detectada em 43,0% das culturas analisadas. A multirresistência aos antimicrobianos foi mais frequente na UTI não COVID-19 (55,7%). A maioria das prescrições de antimicrobianos foram empíricas. **Conclusões:** A recorrência de infecções secundárias e colonizações bacterianas em pacientes com COVID-19 e não COVID-19 em UTIs não devem ser subestimadas. Os perfis de resistência bacteriana elucidados neste estudo destacam a necessidade da implementação de estratégias holísticas e assertivas visando o controle e mitigação dessa problemática, o que contribuirá para a melhoria do prognóstico, bem como, a qualidade e segurança dos pacientes.

Palavras-chave: COVID-19, Coinfecção, Resistência a múltiplos medicamentos, Medicina baseada em evidências.

INTRODUCTION

The World Health Organization considers bacterial resistance to antimicrobial drugs to be the fifth-greatest threat to global health[1]. It is estimated that 700,000 deaths worldwide are associated with infections caused by multidrug-resistant (MDR) microorganisms. This suggests that infections that were previously easily treated could kill approximately 10 million people by 2050[2].

This panorama, in the context of global health, has worsened with the advent of the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has been harmful to various spheres of society. Health services are overloaded with high rates of mortality and morbidity, in addition to social and economic problems[3]. This scenario makes it difficult to meet the targets for mitigating bacterial resistance rates, which makes this problem even more uncertain and further away from a holistic solution[4]. Therefore, bacterial resistance is a problem that accompanies and permeates human evolution and coexists during the pandemic as a threat to global health[5-6].

One of the main complications associated with coronavirus disease 2019 (COVID-19) is severe respiratory dysfunction, which requires intensive treatment with mechanical ventilation support. In this context, the clinical damage described for patients with COVID-19 can be aggravated, especially when there is coinfection or colonization caused by MDRs strains, which results in therapeutic limitations and a worse prognosis, especially in patients hospitalized in the intensive care unit (ICU)[7].

Thus, simply increasing the number of beds is not sufficient to mitigate the increasing mortality rates associated with COVID-19 and complications caused by MDR bacteria, and it is crucial to holistically assess how care is provided[8]. In addition, it is worth mentioning that a study carried out before the pandemic in a medium- and high-complexity hospital in Southeast Pará demonstrated that, of the *Acinetobacter calcoaceticus–baumannii* isolated from hospitalized patients, 55.6% exhibited expression of the blaOXA-23 gene, which is closely associated with resistance to carbapenems, corroborating the relevance of characterizing the profile of bacterial resistance during the pandemic[9].

Therefore, this research is very important, especially considering the direct and indirect damage to the health of patients who are hospitalized in COVID-19 and non-COVID-19 ICUs with bacterial coinfections caused by MDRs strains, such as therapeutic limitations, economic damage associated with overload of the health care industry, and the scarcity of scientific evidence of the occurrence of bacterial resistance during the pandemic in the region. Given this knowledge, it will be possible to direct, in a clear and organized way, strategies for mitigation and control, promoting clarification on the rational use of antimicrobial drugs and the perception of the importance of complying with protocols referring to good care practices in order to break the cycle of dissemination of MDR strains assertively based on local evidence and contribute to national literature.

Thus, the objective of this study was to compare the clinical, epidemiological, and laboratory profiles of bacterial infection or colonization

between patients hospitalized in the COVID-19 ICU and those hospitalized in the non-COVID-19 ICU in Southeast Pará, Brazil.

METHODS

Study type and location

This retrospective analytical study was carried out by analyzing the electronic medical records and microbiological reports of patients admitted to the ICU of a hospital located in the state of Pará in the Brazilian Amazon due to complications associated with COVID-19 and other causes from 2020 to 2021.

This hospital provides medium- and high-complexity services to patients from 15 municipalities in Southeast Pará (Brazil), which belongs to the 12th Regional Health Center (region of Araguaia), has an estimated population of 541.347 inhabitants, and has a population density of 83.46 in hab./km² and an extensive territorial area of 174.174.655 km^2, which corresponds to 14.0% of the total territorial area of Pará[10].

The hospital is located 1.018 km from the capital city and is the main health center in the region. It currently has 105 beds, 90 of which are adult ICU beds. Between July 2020 and October 2020, the maximum number of beds in specific ICUs for COVID-19 was reached, with a total of 18 additional beds. The services offered include general nephrology, hemodialysis, peritoneal dialysis, and kidney transplantation, among others[11].

This study was approved by the research ethics committee (certificate of presentation for ethical assessment no. 54350821.0.0000.8104 and approval opinion no. 5281433) following resolution no. 466 of the National Health Council of December 12, 2012.

Study population

Included in this study were the research data from the medical records of patients hospitalized in COVID-19 or non-COVID-19 ICUs from March 2020 to December 2021 were the positivity of bacteriological cultures of both sexes and age ≥18 years. Those with medical records that did not present information necessary for the research, as well as inaccurate information and incomplete or a lack of antibiogram results, were excluded.

Data extraction

The medical records and microbiological reports were organized chronologically from March 2020 (the beginning of notification of cases in the hospital) to December 2021 in a reserved, well-lit, and noise-free room. For a holistic contemplation of the objectives, the following strategies were applied:

1. Determine the frequency of bacterial resistance to antimicrobial drugs, as well as the main resistance mechanisms, in adult patients hospitalized in the COVID-19 ICU and non-COVID-19 ICU:
   The data present in the laboratory reports of bacteriological cultures and antibiograms were analyzed based on the relationship between the tested drugs and the bacterial susceptibility profile against them. It should be noted that these tests were performed in the hospital's own laboratory and that they duly followed the recommended rigor and were certified by quality control standards. Antimicrobial susceptibility and phenotypic detection of resistance mechanisms were interpreted according to the guidelines of the Brazilian Antimicrobial Susceptibility Testing Committee (BrCAST)[12] each year[9].
2. To describe the occurrence of multidrug-resistant bacteria in COVID-19 and non-COVID-19 ICUs:
   For this, the antibiograms were analyzed, but now considering the classes of antimicrobial drugs tested to classify the bacteria, the strains that exhibited resistance to three or more classes of antimicrobial drugs were called multiresistant[13].
3. Characterize the clinical-epidemiological profile of the patients hospitalized in ICUs infected with or colonized by multidrug-resistant bacteria during the pandemic:
   The variables of sex, housing (rural/urban), hospitalization duration, city of origin, age group, time to a positive culture result, evo-

lution, and comorbidities were evaluated. In addition, from the bacteriological cultures, the variables studied included identification of the bacterial genus, bacterial species, and body site of isolation.

Individuals who presented positive bacteriological cultures at nonsterile sites, such as surveillance swabs, were considered to be colonized. Individuals were considered to be infected based on clinical and laboratory criteria[14-15]. Empirical prescriptions were considered when the use of antimicrobial drugs was based on the most likely agents of infection and clinical characteristics. Evidence-based therapy was defined when the choice of antimicrobial drugs was guided by microbiological tests for microorganisms isolated from the patient, which is a specific therapy[14,16-18].

Statistical analysis

The data obtained in the collection were transferred and tabulated in Microsoft Excel 2019 for further analysis. Descriptive and associative statistical analyses were conducted. For the descriptive analyses, the absolute (N) and relative (%) frequencies were presented for each category of variables analyzed according to the type of ICU: COVID-19 ICU or non-COVID-19 ICU.

For the associative analyses, the relative frequencies of the variables were compared between the patients hospitalized in the COVID-19 ICU and those hospitalized in the non-COVID-19 ICU. When there was a sufficient number of observations in the crossover between each category of variables of interest and the type of ICU, Fisher's exact test was conducted to compare the different groups. Owing to the high number of categories, some variables did not have enough observations to be included in the analysis using this test. In these cases, 95% confidence intervals were generated for each proportion of each category, and the difference between the proportions according to the type of ICU was evaluated based on the overlap of the confidence intervals and estimates between the groups.

All analyses were conducted using Stata 17.0 statistical software (StataCorp LLC, College Station, TX, USA). A significance level of 5% was considered for all analyses.

RESULTS

For the period from March 2020 to December 2021, data from 343 patients colonized by or infected with bacteria were included, 59.5% (204/343) of whom were hospitalized in the COVID-19 ICU and 40.5% (139/343) of whom were hospitalized in the non-COVID-19 ICU. During the study period, 518 bacteriological cultures were obtained, 54.1% (280/518) of which were from patients hospitalized in the COVID-19 ICU and 45.9% (238/518) of which were from patients hospitalized in the non-COVID-19 ICU. In addition, 66.8% (229/343) of the patients included in this study had only one positive culture, whereas 33.2% (114/343) had two or more positive cultures.

Considering the sociodemographic characteristics, most individuals hospitalized in COVID-19 ICU were aged between 42 and 54 years (23.5%), were male (54.9%), and lived in urban areas (91.2%). Patients hospitalized in the non-COVID-19 ICU were more likely to be aged between 54 and 66 years (21.6%); most were male (72.7%) as well, but a higher proportion lived in urban areas (76.3%). Table 1 describes the sociodemographic characteristics of the analyzed study population, as well as the distribution of the patients hospitalized by the type of ICU (COVID-19 ICU or non-COVID-19 ICU). Of the four characteristics evaluated, only skin color did not differ statistically according to the ICU type.

Table 1 summarizes the clinical characteristics of the studied population by comparing the relative frequencies according to ICU type. The distribution of all evaluated variables was different between the COVID-19 ICU and non-COVID-19 ICU patients ($p < 0.05$). The most common hospitalization duration in the COVID-19 ICU patients was fewer than 15 days, whereas that in the non-COVID-19 ICU patients was 15–30 days.

Approximately 64% of patients admitted to the COVID-19 ICU died, while of those admitted to the non-COVID-19 ICU, the frequency of deaths was lower, around 41%. Considering hospital

Table 1. Clinical and sociodemographic profile of patients admitted to the ICU from March 2020 to December 2021 in Pará, Brazil

Variables	COVID-19 ICU		Non-COVID-19 ICU	
	N	%	N	%
Age range (years)	p = 0.004			
18–30	13	6.4	22	15.8
30–42	33	16.2	22	15.8
42–54	48	23.5	16	11.5
54–66	44	21.6	30	21.6
66–78	47	23.0	27	19.4
≥78	19	9.3	22	15.8
Sex			p = 0.001	
Male	112	54.9	101	72.7
Female	92	45.1	38	27.3
Residence zone			p < 0.001	
Urban	186	91.2	106	76.3
Rural	18	8.8	33	23.7
Skin color			p = 0.274	
White	4	2.0	2	1.5
Black	4	2.0	0	0.0
Brown	196	96.1	135	98.5
Hospitalization time (days)			p < 0.001	
<15	120	58.8	49	35.3
15–30	64	31.4	55	39.6
31–45	13	6.4	19	13.7
46–60	7	3.4	9	6.5
≥61	0	0	7	5.0
Grouped comorbidity			p = 0.034	
Circulatory system diseases	96	47.1	57	41.0
Urinary tract diseases	2	1.0	3	2.2
Respiratory system diseases	2	1.0	4	2.9
Nervous system diseases	5	2.5	7	5.0
Endocrine/metabolic diseases	22	10.8	6	4.3
Infectious/parasitic wdiseases	3	1.5	4	2.9
None	74	36.3	55	39.6
Neoplasms	0	0.0	3	2.2
Evolution			p < 0.001	
Hospital discharge	71	34.8	81	58.3
Death	132	64.7	57	41.0
Evasion	1	0.5	0	0
Interhospital transfer	0	0	1	0.7
Origin of infection			p < 0.001	
Internal	43	21.1	48	34.5
Internal MDR	59	28.9	61	43.9
External	44	21.6	12	8.6
External MDR	58	28.4	18	13.0

*Source: own authorship. †The p values were obtained from Fisher's exact test.

discharge, it was found that in the ICU-Covid-19 it was 34.8% and in the non-Covid-19 ICU it was 58.3%.The most prevalent comorbidities in the COVID-19 ICU and non-COVID-19 ICU patients were diseases of the circulatory system (47.1% and 41%, respectively).

Regarding the culture positivity profile, the microbiological characterization of the cultures revealed that, apart from the time to positivity, the other variables were statistically different between the patients of the two types of ICUs. Most (68.1%, 353/518) of the cultures analyzed were obtained from infected patients. The proportion of cultures from infections was higher in the non-COVID-19 ICU patients (56.1%; 198/353) and that of colonization was higher in the COVID-19 ICU patients (75.7%; 125/165). Gram-negative bacteria were the most frequently observed etiological agent in both groups (Covid-19 ICU: 52.9% *versus* non-Covid-19 ICU: 75.2%), with a proportion of 63.1% (327/518) of the cultures analyzed (Table 2).

Regarding the phenotypic profile of resistance, the production of carbapenemases was detected in 43.0% (135/314) of the cultures analyzed, followed by methicillin-resistant *Staphylococcus aureus* (MRSA) being detected in 39.8% (125/314) of the cultures analyzed. In addition, multidrug resistance against antimicrobial drugs was more frequent in the non-COVID-19 ICU patients (55.7%, 137/246) (Table 2).

Table 3 summarizes the comparison of the prescriptions according to the ICU type, considering cultures as the sample unit. It is noted that both in the COVID-19 ICU and in the non-COVID-19 ICU patients, most prescriptions were empirical. However, this percentage was higher in the COVID-19 ICU patients than in the non-COVID-19 patients (83.6% and 60.3%, respectively).

Considering the absolute and relative frequencies of etiological agents according to the ICU type, it was noted that the main bacteria isolated in the COVID-19 ICUs were *S. aureus* (34.3%), followed by *A. calcoaceticus–baumannii* (20.7%). In the non-COVID-19 ICU, the most prevalent strains were *A. calcoaceticus–baumannii* and *Pseudomonas aeruginosa* (18.5%), followed by *S. aureus* (15.1%) (Table 4 and Figure 1).

In Table 5, instead of describing the entire study sample, only the characteristics of the 189 patients who died are described. Of these patients, 69.8% (132/189) were hospitalized in the COVID-19 ICU and 30.2% (57/189) were hospitalized in the non-COVID-19 ICU. Of the variables compared between the COVID-19 and non-COVID-19 ICU

Table 2. Microbiological characterization of positivity for colonization and infection among patients hospitalized in the ICU from 2020 to 2021 in Pará, Brazil

Variables	COVID-19 ICU		Non-COVID-19 ICU	
	N	%	N	%
Positivity time (days)				p = 0.881
<15	176	85.8	118	85.5
15–30	26	12.7	17	12.3
31–45	3	1.5	3	2.2
Infection/colonization				p < 0.001
Infection	155	55.4	198	83.2
Colonization	125	44.6	40	16.8
Sample sites				p < 0.001
Abscess	0	0.0	2	0.8
Abdominal aspirate	0	0.0	1	0.4
Pleural fluid	0	0.0	3	1.3
Catheter tip	6	2.1	7	2.9
Blood	54	19.3	42	17.7
FO secretion	0	0.0	11	4.6
EAR secretion	0	0.0	1	0.4
Tracheal secretion	84	30.0	99	41.6
Urethral secretion	1	0.4	1	0.4
Urine	16	5.7	37	15.6
Surveillance swab	119	42.5	34	14.3
Bacterial group				p < 0.001
Gram-positive	132	47.1	59	24.8
Gram-negative	148	52.9	179	75.2
Phenotypic profile of resistance				p = 0.001
VRE	1	0.5	0	0.0
MRSA	94	47.2	31	27.0
MSSA	2	1.0	5	4.4
ESBL	30	15.1	16	13.9
Carbapenemases	72	36.2	63	54.8
Multidrug resistance				p < 0.001
Yes	109	38.9	137	57.6
No	171	61.1	101	42.4

*Source: own authorship. †The p values were obtained from Fisher's exact test. VRE: vancomycin-resistant enterococci; MSRA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*; ESBL: extended-spectrum beta-lactamase.

Table 3. Comparison of the prescription profiles according to the type of ICU from 2020 to 2021 in Pará, Brazil.

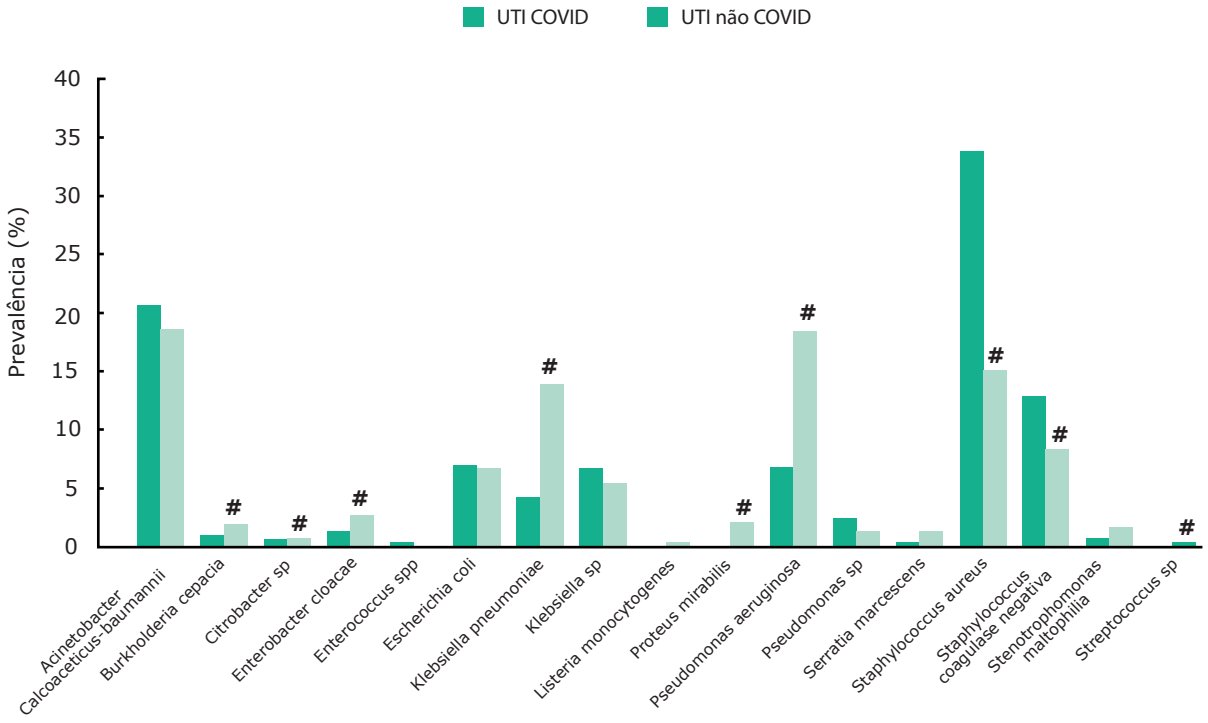
	COVID-19 ICU		Non-COVID-19 ICU	
Prescription	N	%	N	%
				p < 0.001
Empirical	220	83.6	140	60.3
With evidence	43	16.4	92	39.7

*Source: own authorship. †The p values were obtained from Fisher's exact test.

Table 4. Distribution of etiological agents isolated in microbiological cultures of patients hospitalized in the ICU during the COVID-19 pandemic in Pará, Brazil

Etiological agent	COVID-19 ICU			Non-COVID-19 ICU		
	N	%	95% CI	N	%	95% CI
A. calcoaceticus–baumannii	58	20.7	16.4–25.9	44	18.5	14.0–23.9
Burkholderia cepacia†	3	1.1	0.3–3.3	5	2.1	8.7–5.0
Citrobacter sp.†	2	0.7	1.8–2.8	2	0.8	0.2–3.3
Enterobacter cloacae†	4	1.4	0.5–3.8	8	3.4	1.7–6.6
Enterococcus spp.	1	0.4	0.0–2.5	0	0.0	-
Escherichia coli	20	7.1	4.6–10.8	16	6.7	4.2–10.7
Klebsiella pneumoniae†	12	4.3	2.4–7.4	33	13.9	10.0–18.9
Klebsiella sp.	19	6.8	4.4–10.4	13	5.5	3.2–9.2
Listeria monocytogenes	0	0.0	-	1	0.4	0.0–2.9
Proteus mirabilis†	0	0.0	-	5	2.1	0.9–5.0
Pseudomonas aeruginosa†	19	6.8	4.4–10.4	44	18.5	14.0–23.9
Pseudomonas sp.	7	2.5	1.2–5.2	3	1.3	0.4–10.4
Serratia marcescens	1	0.4	0.0–2.5	3	1.3	0.4–10.4
Staphylococcus aureus†	96	34.3	28.9–40.1	36	15.1	11.1–20.3
S. coagulase negativa†	36	12.9	9.4–17.3	20	8.4	5.5–12.7
Stenotrophomonas maltophilia	2	0.7	0.2–2.8	4	1.7	0.6–4.4
Streptococcus sp.†	0	0.0	-	1	0.4	0.1–2.9

*Source: own authorship. †p < 0.05, estimated from the overlapping confidence intervals and estimates.



Source: own authorship. The bars are compared by overlapping their confidence intervals. # represents a statistically significant difference in the relative frequencies between the COVID-19 ICU patients and non-COVID-19 ICU patients ($p < 0.05$).

Figure 1. Prevalence of isolated etiological agents among patients admitted to the ICU from 2020 to 2021 in Pará, Brazil.

patients, the total duration of hospitalization, sample site, etiological agent, multidrug resistance, and prescription were statistically different.

Among the patients who died, there was a higher proportion of multidrug resistance in the non-COVID-19 ICU patients (57.9%), with the majority of patients in both ICUs having comorbidities (80.9%, 127/157; in some cases, the field was ignored), the cultures most frequently came from infections (62.4%, 118/189), the prescription of antimicrobial drugs was empirically performed in 77.2% (146/189) of the cases, and the most frequent etiological agents were *S. aureus* (32.3%, 61/189) and *A. calcoaceticus–baumannii* (23.3%, 44/189) (Table 5).

DISCUSSION

It is noteworthy that the occurrence of secondary infections or colonization among ICU patients is a serious and persistent public health problem, as demonstrated in a study in which the mortality in ICU patients diagnosed with some type of *Acinetobacter* sp. infection was 50%, and that among colonized patients was 13.6%, with a total mortality of 30%[19]. Corroborating this fact, in this study, most patients hospitalized in the ICU (either ICU type) were infected, and a high proportion of those in the non-COVID-19 ICU were infected.

In addition, it is emphasized that the problem associated with the occurrence of healthcare-associated infections (HAIs) permeates and tends to persist before, during, and after the pandemic. This can be confirmed by analyzing local scientific evidence of the occurrence, colonization, and bed contamination rates of HAIs prior to and during the COVID-19 pandemic period[9,20].

Furthermore, from the analysis of sociodemographic, clinical, and available data in the literature, it is possible to infer that infections or colonization occurs mainly in patients with severe underlying disease and a poor prognosis,

Table 5. Characteristics of the subpopulation of patients admitted to the ICU who died in the period from 2020 to 2021 in Pará, Brazil.

Variables	COVID-19 ICU		Non-COVID-19 ICU	
	N	%	N	%
Age range (years)				p = 0.247
18–30	7	5.3	5	8.8
30–42	14	10.6	3	5.3
43–54	27	20.5	8	14.0
55–66	34	25.8	16	28.1
67–78	33	25.0	11	19.3
≥79	17	12.9	14	24.6
Total hospitalization time (days)				p = 0.007
<15	77	58.3	22	38.6
15–30	47	35.6	24	42.1
31–45	5	3.8	4	7.0
46–60	3	2.3	4	7.0
≥61	0	0.0	3	5.3
Presence of comorbidity				p = 0.569
No	20	19.1	10	19.2
Yes	85	80.9	42	80.8
Sample Site				p = 0.002
Abscess	0	0.0	1	1.8
Pleural fluid	0	0.0	1	1.8
Catheter tip	1	0.8	0	0.0
Blood	25	18.9	5	8.8
FO secretion	0	0.0	1	1.8
Tracheal secretion	46	34.9	25	43.9
Urethral secretion	1	0.8	0	0.0
Urine	4	3.0	8	14.0
Surveillance swab	55	41.7	16	28.1
Classification				p = 0.053
Infection	77	58.3	41	71.9
Colonization	55	41.7	16	28.1
Etiological agent				p = 0.004
A. calcoaceticus–baumannii	33	25.0	11	19.3
Citrobacter sp.	0	0.0	1	1.8
Enterobacter cloacae	1	0.8	3	5.3
Enterococcus spp.	1	0.8	0	0.0
Escherichia coli	6	4.6	6	10.5
Klebsiella pneumoniae	5	3.8	5	8.8
Klebsiella sp.	9	6.8	5	8.8
Proteus mirabilis	0	0.0	3	5.3
Pseudomonas aeruginosa	10	7.6	5	8.8
Pseudomonas sp.	5	3.8	0	0.0
Serratia marcescens	0	0.0	1	1.8
Staphylococcus aureus	48	36.4	13	22.8
S. coagulase negativa	14	10.6	3	5.3
Stenotrophomonas maltophilia	0	0.0	1	1.8
Phenotypic profile of resistance				p = 0.767
VRE	1	1.0	0	0.0
MRSA	14	13.9	13	37.1
MSSA	1	1.0	0	0.0
ESBL	14	13.9	6	17.1
Carbapenemases	38	37.6	16	45.7
Multidrug resistance				p = 0.025
No	80	60.6	24	42.1
Yes	52	39.4	33	57.9
Prescription				p = 0.040
Empirical	107	84.9	39	70.9
With evidence	19	15.1	16	29.1

*Source: own authorship. †The p values were obtained from Fisher's exact test

continue...

those who undergo invasive procedures, such as mechanical ventilation, those with an advanced age, those who use of broad-spectrum antibiotics, and those who are hospitalized in the ICU[21-22]. Therefore, the high incidence of colonization detected in this study in patients hospitalized in the COVID-19 ICU can be considered a predisposing factor for the occurrence of HAIs, as has already been demonstrated in the literature[21-23].

Thus, it is necessary to emphasize the impact of HAIs on this problem, as they occur when there are failures in the execution of assistance protocols through cross-contamination, increasing the spread of MDR bacteria and SARS-CoV-2, causing outbreaks that are difficult to control and with immeasurable damage, such as increased mortality and morbidity rates. During the pandemic, this may have been driven by an overload of health professionals[3,7].

Corroborating this fact, a nosocomial outbreak caused by the transmission of SARS-CoV-2 has a mortality rate of approximately 60%[7,24]. Another study carried out in Rio de Janeiro revealed that the detection of MDR bacteria was considered a risk factor for death (p= 0.04) and was correlated with approximately 40% of deaths. In addition, the mortality rate associated with mechanical ventilation was high (60%)[8].

In terms of the etiological agent, it was observed that the most prevalent strains were bacteria belonging to the group called "ESKAPE," which are opportunistic bacteria with a high degree of pathogenicity and are considered a priority target for the formulation of new drugs and strategies for control[25]. In this context, due to the high selective pressure caused by the use of antimicrobial drugs

and disinfectants, ICUs are important sources for the origin and transmission of MDR pathogens, and it is essential to understand the epidemiological and susceptibility profiles of colonization and infections caused by these strains[26]

In addition, a high number of *A. calcoaceticus-baumannii,* belonging to the ESKAPE group, and *Staphylococcus aureus*, were observed in patients admitted to the COVID ICU. Thus, it was found that patients with COVID admitted to the ICU were more prone to bacterial coinfections by these etiological agents. Different factors can influence the appearance of these etiological agents, such as variables related to demographic characteristics (age, sex, etc.), length of stay or clinical conditions (for example, presence of comorbidities) that increase the risk, although not consistently.

Thus, the results of the phenotypic analyses associated with bacterial resistance reported in this study deserve attention, as they demonstrate a higher prevalence of carbapenemase production and detection of MRSA, which may explain the high level of bacterial multiresistance observed. This can be explained by the ability of gram-negative bacteria to produce enzymes that hydrolyze antimicrobial compounds, such as carbapenemases, which are encoded by plasmids with a high transmission rate. These enzymes tend to inactivate carbapenems prior to their therapeutic effect[27].

Therefore, it is crucial to highlight that these drugs are among the last therapeutic options for the treatment of serious infections caused by drug-resistant gram-negative bacteria, and the spread of drug-resistant bacteria is a growing concern[28]. In addition, MRSA infections are a threat to global health, as antibiotic resistance continues to develop, making clinical treatment difficult[29].

Furthermore, MRSA resistance mechanisms are complex and mainly involve three aspects: an alteration in cell membrane permeability, alteration in the efflux system, and excessive production of β-lactamases enzymes[30]. It can be considered a particularly deadly pathogen because it has a large reservoir of virulence factors and immune evasion molecules associated with antimicrobial resistance, resulting in a poorer prognosis[29].

The presence of colonization or infection may be associated with poor outcomes in ICU patients, including increased mortality. Russo[31] demonstrated that colonization by *A. baumannii* was much higher in patients admitted to the COVID-19 ICU (63%) than in patients admitted to the non-COVID-19 ICU (8%), which corroborates the findings of this research study. In addition, a mortality rate of as high as 64.7% has been reported in patients with *A. baumannii* admitted to the COVID-19 ICU[32].

Another study carried out in São Paulo demonstrated that MRSA infection increased during the pandemic compared with the pre-pandemic scenario[33]. Consistent with this information, approximately five-times higher rates of bacteremia caused by MRSA were observed in patients with COVID-19 than in patients without COVID-19 in a survey[34-35]. In addition, the impact of the difficulties associated with the proper management of COVID-19 was also evidenced in this study, by demonstrating a high frequency of empirical prescriptions in the COVID-19 ICU, that is, prescriptions without laboratory evidence of bacterial coinfection[34-35].

This reinforces the idea that a high level of empirical prescriptions can contribute to greater selective pressure and the advent of outbreaks caused by multidrug-resistant strains. As demonstrated in a meta-analysis, in which the majority of patients with COVID-19 received antibiotics (71.9%) despite the rates of bacterial coinfection (3.5%) and secondary infections (14.3%), not justifying this measure, as they are much smaller, may directly reflect the higher occurrence of HAIs in hospitals and a poorer prognosis. Colonizations can precede the occurrence of infections, however, compliance with good care practices can prevent this from happening. Therefore, the use of antimicrobials in case of colonization is not justified.[36-38].

The results of this study corroborate that most patients who died received empirical prescriptions for antimicrobial drugs. In addition to clinical harm, antimicrobial prescriptions for colonized patients or patients with HAI increase hospital expenses, including expenses related to pharmacies, laboratory tests, and the period of hospitalization[38]. By 2050, the global capital loss caused by antibiotic resistance is estimated to be approximately $300 billion USD to $1 trillion USD[39]. In this context, a study reported an economic loss per capita attributed to HAIs of $2047.07 USD, mainly for pharmaceutical costs ($1044.39 USD)[40].

Therefore, mainly by evaluating the scientific evidence described at the local level about the recurrent occurrence of infections and colonization caused by MDR bacteria, it is crucial that strategic measures aimed at prevention, improvement in the quality of health care, and improvement in patient safety can be implemented[9,20], applying good practices to control and mitigate these problems already validated. Thus, contact precautions, active surveillance cultures, monitoring, auditing and measurement feedback, hand hygiene, environmental cleanliness, and antimicrobial use management can be cited[19-20].

The limitations of this study are its retrospective nature, in which selection bias or residual confounding cannot be excluded. In addition, this was not a multicenter study, as it was restricted to a single hospital and, thus, it may present a specific microbiological and antibiotic profile at this site. Another limitation was the unavailability of more detailed data on the empirical use of antimicrobials, which limited the assessment of their impact on the development of secondary infections.

CONCLUSION

Based on the evidence presented, it is possible to determine that infections were more common in patients hospitalized in the non-COVID-19 ICU and colonization in patients with complications from COVID-19. Bacteria belonging to the ESKAPE group were the most prevalent, particularly *S. aureus* and *A. baumannii.* Notably, it was possible to demonstrate the similar and frequent occurrence of bacterial multidrug resistance, as well as the phenotypic detection of carbapenemases and MRSA strains. In addition, empirical therapy was highly frequent among patients who died.

Thus, the recurrence of secondary infections and bacterial colonization in COVID-19-hospitalized patients and non-COVID-19-hospitalized patients should not be underestimated. Knowledge of the clinical, microbiological, and bacterial resistance profiles reveals the need to formulate holistic and assertive strategies to control and mitigate these problems, contributing to better prognosis and improvement of the quality of life and safety of patients.

REFERENCES

1. World Health Organization. Antimicrobial resistance [Internet]. Who.int. World Health Organization: WHO; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
2. Barber S, Sutherland N. DEBATE PACK O'Neill Review into Antibiotic Resistance [Internet]. 2017. Available from: https://researchbriefings.files.parliament.uk/documents/CDP-2017-0074/CDP-2017-0074.pdf
3. Nicola M, Alsafi Z, Sohrabi C, et al. The socio-economic implications of the coronavirus and COVID-19 pandemic: a review. Int J Surg. 2020;78(78):185–93. https://doi.org/10.1016/j.ijsu.2020.04.018.
4. Knight GM, Glover RE, McQuaid CF, et al. Antimicrobial resistance and COVID-19: intersections and implications. eLife. 2021;10(1):1–27. https://doi.org/10.7554/eLife.64139.
5. Bhullar K, Waglechner N, Pawlowski A, Koteva K, Banks ED, Johnston MD, et al. Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome. PLoS ONE. 2012;7(4):1–11. https://doi.org/10.1371/journal.pone.0034953.
6. World Health Organization. 10 global health issues to track in 2021 [Internet]. www.who.int. 2020. Available from: https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021#:~:text=Speed%20up%20access%20to%20COVID
7. Mimura K, Oka H, Sawano M. A perspective on hospital-acquired (nosocomial) infection control of COVID-19: usefulness of spatial separation between wards and airborne isolation unit. Journal of Breath Research. 2021;15(4):042001. https://doi.org/10.1088/1752-7163/ac1721.
8. Provenzano BC, Bartholo T, Ribeiro-Alves M, Santos APGD, Mafort TT, Castro MCS de, et al. The impact of healthcare-associated infections on COVID-19 mortality: a cohort study from a Brazilian public hospital. Revista Da Associacao Medica Brasileira. 2021;67(7):997–1002. https://doi.org/10.1590/1806-9282.20210433.
9. Ribeiro EA, Gales AC, Oliveira APS de, Coelho DD, Oliveira RA de, Pfrimer IAH, et al. Molecular epidemiology and drug resistance of Acinetobacter baumannii isolated from a regional hospital in the Brazilian Amazon region. Revista da Sociedade Brasileira de Medicina Tropical. 2021;54(1):1–5. https://doi.org/10.1590/0037-8682-0087-2020.
10. Instituto Brasileiro de Geografia e Estatística. Pará | Cidades e Estados | IBGE [Internet]. www.ibge.gov.br. 2021. Available from: https://www.ibge.gov.br/cidades-e-estados/pa/
11. Hospital Regional Público do Araguaia. Hospital Regional Público do Araguaia [Internet]. HRPA. 2021. Available from: https://www.hrpa.org.br/
12. Brazilian Committee on Antimicrobial Susceptibility Testing. BR Cast [Internet]. BrCAST. 2021. Available from: http://brcast.org.br/documentos/
13. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for

acquired resistance. Clinical Microbiology and Infection: the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases. 2012;18(3):268–81. https://doi.org/10.1111/j.1469-0691.2011.03570.x.

14. Agência Nacional de Vigilância Sanitária. Série Segurança do Paciente e Qualidade em Serviços de Saúde Critérios Diagnósticos de Infecção Relacionada à Assistência à Saúde [Internet]. 2013. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/criterios_diagnosticos_infeccoes_assistencia_saude.pdf

15. Martín-Aspas A, Guerrero-Sánchez FM, García-Colchero F, Rodríguez-Roca S, Girón-González J-A. Differential characteristics of Acinetobacter baumannii colonization and infection: risk factors, clinical picture, and mortality. Infection and Drug Resistance. 2018;11(1):861–72. https://doi.org/10.2147/idr.s163944.

16. Leekha S, Terrell CL, Edson RS. General Principles of Antimicrobial Therapy. Mayo Clinic Proceedings. 2011;86(2):156–67. https://doi.org/10.4065/mcp.2010.0639.

17. Agência Nacional de Vigilância Sanitária. Diretriz Nacional para Elaboração de Programa de Gerenciamento do Uso de Antimicrobianos em Serviços de Saúde. GVIMS/GGTES/ANVISA [Internet]. 2017. Available from: http://antigo.anvisa.gov.br/documents/33852/271855/Diretriz+Nacional+para+Elabora%C3%A7%C3%A3o+de+Programa+de+Gerenciamento+do+Uso+de+Antimicrobianos+em+Servi%C3%A7os+de+Sa%C3%BAde/667979c2-7edc-411b-a7e0-49a6448880d4?version=1.0

18. World Health Organization. Antimicrobials tewrdship programmes in health-care facilities in low-and middle-income countries a who practical toolkit antimicrobial stewardship [Internet]. 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/329404/9789241515481-eng.pdf

19. Huang H, Chen B, Liu G, Ran J, Lian X, Huang X, et al. A multi-center study on the risk factors of infection caused by multi-drug resistant Acinetobacter baumannii. BMC Infectious Diseases. 2018;18(1):1–6. https://doi.org/10.1186/s12879-017-2932-5.

20. Ribeiro EA, Carneiro TL, Andrade AL, Alves JAG. Ocorrência de contaminações por bactérias multirresistentes em leitos hospitalares na Amazônia durante a pandemia de COVID-19. Saúde (Santa Maria). 2021;47(1):1–14. https://doi.org/10.5902/2236583463270.

21. Hoang S, Georget A, Asselineau J, Venier A-G, Leroyer C, Rogues AM, et al. Risk factors for colonization and infection by Pseudomonas aeruginosa in patients hospitalized in intensive care units in France. PLoS One. 2018;13(3):e0193300. https://doi.org/10.1371/journal.pone.0193300.

22. Falcone M, Tiseo G, Giordano C, Leonildi A, Menichini M, Vecchione A, et al. Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: a prospective observational study. Journal of Antimicrobial Chemotherapy. 2020;76(4):1078–84. https://doi.org/10.1093/jac/dkaa530.

23. Blot S, Ruppé E, Harbarth S, Asehnoune K, Poulakou G, Luyt C-E, et al. Healthcare-associated infections in adult intensive care unit patients: Changes in epidemiology, diagnosis, prevention and contributions of new technologies. Intensive and Critical Care Nursing. 2022;70(1):103227. https://doi.org.10.1016/j.iccn.2022.103227.

24. Abbas, M., Robalo Nunes, T., Martischang, R. et al. Nosocomial transmission and outbreaks of coronavirus disease 2019: the need to protect both patients and healthcare workers. Antimicrob Resist Infect Control 10, 7 (2021). https://doi.org/10.1186/s13756-020-00875-7

25. Oliveira DMP, Forde BM, Kidd TJ, Harris PNA, Schembri MA, Beatson SA, et al. Antimicrobial Resistance in ESKAPE Pathogens. Clinical Microbiology Reviews. 2020;33(3):1–13. https://doi.org/10.1128/CMR.00181-19.

26. Cureño-Díaz MA, Durán-Manuel EM, Cruz-Cruz C, Ibáñez-Cervantes G, Rojo-Gutiérrez MI, Moncayo-Coello CV, et al. Impact of the modification of a cleaning and disinfection method of mechanical ventilators of COVID-19 patients and ventilator-associated pneumonia: One year of experience. American Journal of Infection Control. 2021;49(12):1474–80. https://doi.org/ 10.1016/j.ajic.2021.09.012.

27. Bonomo RA, Burd EM, Conly J, Limbago BM, Poirel L, Segre JA, et al. Carbapenemase-Producing Organisms: A Global Scourge. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2018;66(8):1290–7. https://doi.org/10.1093/cid/cix893.

28. Nordmann P, Poirel L. Epidemiology and Diagnostics of Carbapenem Resistance in Gram-negative Bacteria. Clinical Infectious Diseases. 2019;69(7):S521–8. https://doi.org/10.1093/cid/ciz824.

29. Guo Y, Song G, Sun M, Wang J, Wang Y. Prevalence and Therapies of Antibiotic-Resistance in Staphylococcus aureus. Frontiers in Cellular and Infection Microbiology. 2020;10(1):1–11. https://doi.org/10.3389/fcimb.2020.00107.

30. Vestergaard M, Frees D, Ingmer H. Antibiotic Resistance and the MRSA Problem. Microbiology Spectrum. 2019;7(2):1–23. https://doi.org/10.1128/microbiolspec.gpp3-0057-2018.

31. Russo A, Gavaruzzi F, Ceccarelli G, Borrazzo C, Oliva A, Alessandri F, et al. Multidrug-resistant Acinetobacter baumannii infections in COVID-19 patients hospitalized in intensive care unit. Infection. 2021;50(1):83–92. https://doi.org/10.1007/s15010-021-01643-4.

32. Montrucchio G, Corcione S, Lupia T, Shbaklo N, Olivieri C, Poggioli M, et al. The Burden of Carbapenem-Resistant Acinetobacter baumannii in ICU COVID-19 Patients: A Regional Experience. Journal of Clinical Medicine. 2022;11(17):5208. https://doi.org/10.3390/jcm11175208.

33. Polly M, de Almeida BL, Lennon RP, Cortês MF, Costa SF, Guimarães T. Impact of the COVID-19 pandemic on the incidence of multidrug-resistant bacterial infections in an acute care hospital in Brazil. American Journal of Infection Control. 2022;50(1):32–8. https://doi.org/10.1016/j.ajic.2021.09.018.

34. Aslam S, Asrat H, Liang R, Qiu W, Sunny S, Maro A, et al. Methicillin-resistant *Staphylococcus aureus* bacteremia during the coronavirus disease 2019 (COVID-19) pandemic: Trends and distinguishing characteristics among patients in a healthcare system in New York City. Infection Control & Hospital Epidemiology. 2022;1–3. https://doi.org/10.1017/ice.2022.238.

35. Habib G, Mahmood K, Gul H, Tariq M, Ain QU, Hayat A, et al. Pathophysiology of Methicillin-Resistant Staphylococcus aureus Superinfection in COVID-19 Patients. Pathophysiology. 2022;29(3):405–13. https://doi.org/10.3390/pathophysiology29030032.

36. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clinical Microbiology and Infection. 2020;26(12):1622–9. https://doi.org/10.1016/j.cmi.2020.07.016.

37. Souza SCS, Silva DF da, Belei RA, Carrilho CMD de M. Fatores associados à mortalidade de pacientes com enterobactéria resistente aos carbapenêmicos. Medicina (Ribeirão Preto) [Internet]. 2 de abril de 2016 [citado 23 de outubro de 2022];49(2):109-15. Disponível em: https://www.revistas.usp.br/rmrp/article/view/118394

38. Zhen X, Stålsby Lundborg C, Sun X, Zhu N, Gu S, Dong H. Economic burden of antibiotic resistance in China: a national level estimate for inpatients. Antimicrobial Resistance & Infection Control. 2021;10(5):1–9. https://doi.org/10.1186/s13756-020-00872-w.

39. Burki TK. Superbugs: An Arms Race Against Bacteria. The Lancet Respiratory Medicine. 2018;6(9):668. https://doi.org/10.1016/s2213-2600(18)30271-6.

40. Li P, Li Y, Zhang Y, Bao J, Yuan R, Lan H, et al. Economic burden attributable to healthcare-associated infections in tertiary public hospitals of Central China: a multi-centre case-control study. Epidemiology and Infection. 2022;150(1):1–4. https://doi.org/10.1017/s0950268822001340.

Author's contributions

MPM, MTC and LLN participated in the conceptualization, data curation, formal analysis, investigation, writing of the original draft and writing of the editing of the manuscript.
EAR, main author, participated in the conceptualization, data curation, formal analysis, investigation, editation, management and revisation the manuscript.
MJR participated in the conceptualization, data curation, formal analysis, investigation, editation and revisation the manuscript.
All authors approved the final version of the article.

Funding

There was no funding.

Acknowledgements

We thank the Higher Education College of the Reunited Amazon. We thank the *Hospital Regional Público do Araguaia* for providing the data for the research and *Causale Consultoria* for assisting in the statistical analysis and interpretation of results.

Corresponding Author:
Edlainny Araujo Ribeiro
dyy_araujo77@hotmail.com

Editor:
Prof. Dr. Felipe Villela Gomes

Received: nov 15, 2022
Approved: apr 24, 2023