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Analysis of Healthcare-Associated Infections in COVID-19 patients admitted to an Intensive Care Unit

Análise das Infecções Relacionadas à Assistência à Saúde em pacientes com COVID-19 internados em uma Unidade de Terapia Intensiva

Análisis de las Infecciones Relacionadas con la Asistencia Sanitaria en pacientes con COVID-19 ingresados en una Unidad de Cuidados Intensivos

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Abstract
Introduction: Healthcare-associated infections (HAIs) are a major public health problem. **Objective:** To evaluate the profile of SAIs in patients with COVID-19 admitted to the intensive care unit (ICU) in a public hospital in southern Brazil. Method: Cross-sectional, retrospective study, conducted between March 2020 to October 2021, of patients with COVID-19 hospitalized in ICU with IRAS. Results: The main infection was ventilator-associated pneumonia (230 cases), followed by urinary tract infections (160 cases) and bloodstream infections (103 cases), associated with the presence of catheter. Regarding the main microorganisms, the high prevalence of multidrug-resistant *Acinetobacter baumannii* (112 cases) was noteworthy in ventilator-associated pneumonia, with an increasing increase in the analyzed period. The expressiveness of fungal infections, especially *Candida albicans*, was evidenced. Patients with ventilator-associated pneumonia had lower mortality rates (OR= 0.31; p= 0.034), which increased significantly with increasing days of ICU stay (OR= 3.02; p= 0.0000007). The profile of the patients was mainly male, with significant use of antimicrobials and antifungals, high degree of pulmonary impairment, with evolution to death. Among the predictors of mortality, the most impacting was acute renal failure (OR= 4.45; p=0.0002) and the least related was pulmonary thromboembolism (OR=0.47; p= 0.0167). Conclusion: The high percentage of bacterial and fungal IRAS was evidenced. The highest mortality predictor was acute renal failure, while the lowest mortality was pulmonary thromboembolism.
Keywords: Cross infection; COVID-19; SARS-CoV-2; Intensive care units; Catheter-associated infections; Infection control.

Resumo
Introdução: As infecções relacionadas à assistência à saúde (IRAS) são um grave problema de saúde pública. Objetivo: Avaliar o perfil das IRAS em pacientes com COVID-19 internados em unidade de terapia intensiva (UTI) em um hospital público da região Sul do Brasil. Método: Estudo transversal, retrospectivo, realizado entre março de 2020 a outubro de 2021, de pacientes com COVID-19 hospitalizados em UTI com IRAS. Resultados: A principal infecção foi a pneumonia associada a ventilação mecânica (230 casos), seguida de infecções do trato urinário (160 casos) e de corrente sanguínea (103 casos), associadas à presença de cateter. Em relação aos principais microrganismos, destacou-se a alta prevalência do *Acinetobacter baumannii* multirresistente (112 casos) nas pneumonias associadas à ventilação mecânica com um aumento crescente no período analisado. Evidenciou-se a expressividade das infecções fúngicas, destacando-se a *Candida albicans*. Os pacientes com pneumonia associada à ventilação mecânica apresentaram menores taxas de mortalidade (OR= 0,31; p= 0,034), que aumentaram significativamente com o aumento de dias de internamento em UTI (OR= 3,02; p= 0,0000007). O perfil dos pacientes era principalmente de homens, com uso expressivo de antimicrobianos e antifúngicos, alto grau de comprometimento pulmonar, com evolução para óbito. Entre os fatores preditores de mortalidade, o mais impactante foi a insuficiência renal aguda (OR= 4,45; p=0,0002) e o de menor relação foi o tromboembolismo pulmonar (OR=0,47; p= 0,0167). Conclusão: Evidenciou-se o alto percentual de IRAS bacterianas e fúngicas. O maior fator preditor de mortalidade foi a insuficiência renal aguda, enquanto o de menor mortalidade foi o tromboembolismo pulmonar.
Palavras-chave: Infecção hospitalar; COVID-19; SARS-CoV-2; Unidade de terapia intensiva; Infecções relacionadas a cateter; Controle de infecções.

Resumen
Introducción: Las infecciones asociadas a la asistencia sanitaria (IAAS) constituyen un importante problema de salud pública. Objetivo: Evaluar el perfil de las IAAS en pacientes con COVID-19 ingresados en la unidad de cuidados intensivos (UCI) en un hospital público del sur de Brasil. Método: Estudio transversal, retrospectivo, realizado entre marzo de 2020 y octubre de 2021, de pacientes con COVID-19 hospitalizados en UCI con IRAS. Resultados: La principal infección fue la neumonía asociada al ventilador (230 casos), seguida de infecciones del tracto urinario (160 casos) e infecciones del torrente sanguíneo (103 casos), asociadas a la presencia de catéter. En cuanto a los principales microorganismos, destacó la alta prevalencia del *Acinetobacter baumannii* multirresistente (112 casos) en la neumonía asociada a ventilador con un aumento creciente en el periodo analizado. Las infecciones fúngicas fueron expresivas, especialmente *Candida albicans*. Los pacientes con neumonía asociada a ventilador presentaron menor mortalidad (OR= 0,31; p= 0,034), que aumentó significativamente con el incremento de días de estancia en UCI (OR= 3,02; p= 0,0000007). El perfil de los pacientes fue mayoritariamente masculino, con uso significativo de antimicrobianos y antifúngicos, alto grado de afectación pulmonar y evolución a muerte. Entre los predictores de mortalidad, el más impactante fue la insuficiencia renal aguda (OR= 4,45; p=0,0002) y el menos relacionado el tromboembolismo pulmonar (OR=0,47; p= 0,0167). Conclusión: Se evidenció el alto porcentaje de IRAS bacterianas y fúngicas. El mayor predictor de mortalidad fue la insuficiencia renal aguda, mientras que el de menor mortalidad fue el tromboembolismo pulmonar.
Palabras clave: Programa de control de infecciones hospitalarias; COVID-19; SARS-CoV-2; Unidades de cuidados intensivos; Infecciones relacionadas con cateteres; Control de infecciones.

1. Introduction

In January 2020, the World Health Organization (WHO) declared COVID-19 a global health emergency only one month after its appearance in Wuhan, China. In March of the same year, it was recognized as a pandemic due to its rapid spread on a global scale (WHO, 2021). It consists of a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belonging to the same family as SARS-CoV and MERS-CoV, the causative agents of other major epidemics in recent decades (Cucinotta & Vanelli, 2020). By January 2023, 656,398,043 cases of COVID-19 have been reported worldwide and more than 6.6 million deaths according to WHO as of January 1, 2023 (WHO, 2023).

Since its onset, the pandemic has placed strenuous demands on the healthcare system, which resulted in modifications in routine patient care practices, potentially increasing or decreasing healthcare-associated infections (HAIs) (Baker et al., 2022). WHO defines it as an infection that is acquired by the patient during hospital admission or care in another healthcare facility, which was not present or incubating at the time of admission (WHO, 2016). For standardization, the National Health Surveillance Agency (ANVISA), a Brazilian national control agency, determined that infections occurring after the third day of hospitalization should be considered as HAIs (ANVISA, 2021).

A review and meta-analysis by Louise, Benjamin, and Vadsala (2020) found a 14% prevalence of bacterial co-infections in Intensive Care Unit (ICU) patients. Among other findings, the presence of pathological agents such as *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Chlamydia sp.*, *Enterococcus faecium*, Methicillin-resistant *Staphylococcus aureus* (MRSA) and fungi such as *Candida albicans*, *Candida glabrata* and *Aspergillus sp.* This becomes worrisome as longer hospital stays have been correlated to an emergence of multidrug-resistant microorganisms (O'Toole, 2021). According to the Centers for Disease Control and Prevention (CDC), a public health agency in the United States, an increase in the number of HAIs has been observed in 2021 due to the impact of COVID-19 on healthcare systems, ranging from a 30 to 65% increase in ventilator-associated infections, catheter-associated urinary tract infections and bloodstream infections (Lastinger et al., 2022).

Therefore, this study aimed to evaluate the profile of bacterial and fungal infections associated with healthcare in patients with COVID-19 admitted to the Intensive Care Unit (ICU) during the pandemic in the University Hospital of the State University of Ponta Grossa (HU-UEPG). As secondary objectives, we also determined the incidence at different sites of infection, the profile of microorganisms and the incidence of multidrug-resistant microorganisms, as well as the treatment chosen and the frequency of antimicrobial use. It was also possible to evaluate if the presence of specific comorbidities were determinants of longer hospitalization and mortality.

2. Methodology

This is a cross-sectional retrospective study, done in the University Hospital of the State University of Ponta Grossa (HU-UEPG), state of Paraná, in southern Brazil. It was approved by the hospital's and the university's Research Ethics Committee under the protocol numbered 4.110.874. To select the patients whose medical records would be analyzed, a spreadsheet containing the notifications of all HAIs that had occurred in the hospital organized by the Epidemiology and Hospital Infection Control Nucleus (EHICN) was consulted.

HAIs were considered infections contracted three days after the individual's entry in the hospital, in patients with a confirmed diagnosis of COVID-19 and who were in the Intensive Care Unit (ICU). The diagnosis of COVID-19 was confirmed by rapid test, serology or RT-PCR (real time reverse transcriptase-polymerase chain reaction). All HAIs that occurred during the period from March 2020 to October 2021 and met these criteria were included. Patient data was collected through electronic medical records, from GSUS (Hospital and Outpatient Management System of the Unified Health System) and Philips Tasy®, since the hospital switched systems during the pandemic period.

Information was collected regarding the type of infection presented. When present in the urinary tract, they were classified as Catheter-Associated Urinary Tract Infections (CAUTI) and Non-Catheter-Associated Urinary Tract Infections (NCAUTI). Bloodstream infections were also dichotomized according to the presence of a central venous catheter into Catheter-Associated Bloodstream Infection (CABSI) and Non-Catheter-Associated Bloodstream Infection (NCABSI). In respiratory site infections, there was a separation regarding Tracheobronchitis, Ventilator-Associated Pneumonia (VAP) and Pneumonia not associated with mechanical ventilation (PNM).

The etiological agents and the presence of antimicrobial resistance were also pointed out. Bacterial and fungal samples were isolated from different anatomical sites and identification of pathogens was performed using standardized microbiological procedures in the hospital's laboratory. Epidemiological data was obtained regarding the patient, such as age, gender, comorbidities (smoking, alcoholism, diabetes, hypertension, dyslipidemia, obstructive sleep apnea syndrome, chronic kidney disease, benign prostatic hyperplasia, obesity, heart disease, chronic obstructive pulmonary disease, among others). In addition, data regarding the outcome (deaths, transfers and hospital discharges), use of antimicrobials, antifungals, corticosteroids and other medications were computed. Finally, the length of stay in the ICU, mechanical ventilation, tracheostomy, indwelling urinary catheter, central venous catheter and use of invasive blood pressure were also evaluated.

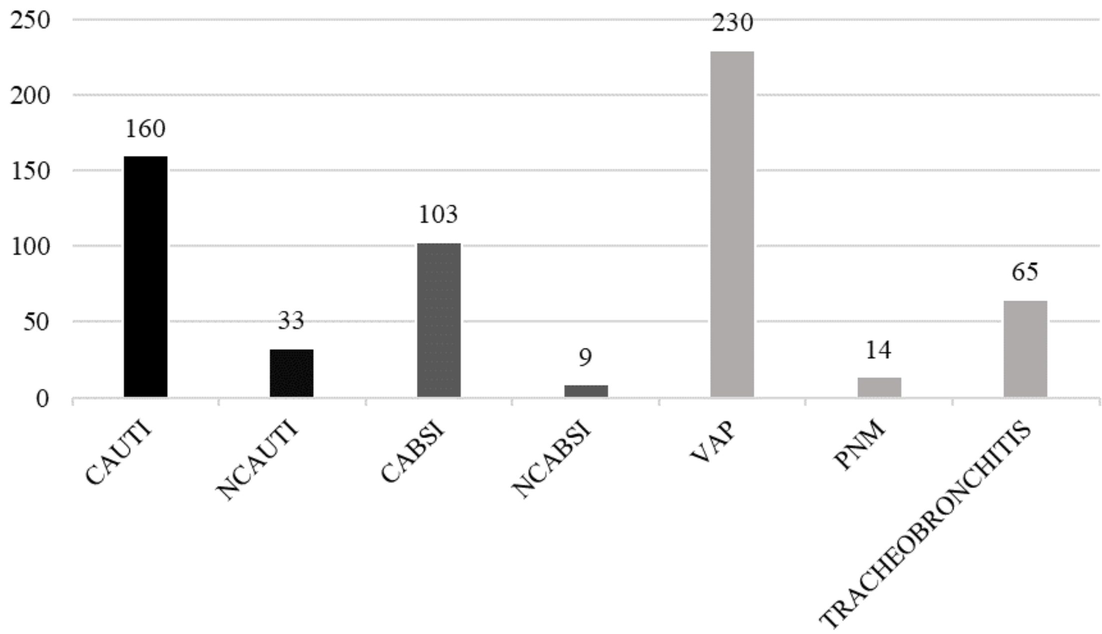
After collecting data from 408 patients, statistical analysis was performed using the software Epi Info 7.2.5.0. Results were expressed in absolute and relative frequencies, described in the text and throughout graphs and tables. All variables were tested for normality with the Kolgomorov Smirnov test. Categorical variables were compared using the Chi-square and Fischer test. Continuous variables were analyzed using Student's t-test for normal and Mann- Whitney test for non-normal. The normal variables were displayed in mean and the non-normal variables in median.. To correlate comorbidities with prolonged hospitalization days (≥20 days) and mortality, logistic regression was performed and p values < 0.05 were considered significant. The 20-day cut-off was defined from the average length of ICU stay found in the study. The odds ratio was calculated at a 95% confidence interval.

3. Results

Data from 408 patients was analyzed. The highest percentage of HAIs in the analyzed period was in the second quarter of 2021 (39.41%), followed by the first quarter of 2021 (21.67%) and the third quarter of 2021 (17.98%), which are considered as the peak of the highest number of cases of COVID-19 infection in the institution under study. The mean age of the patients was 56.85 years, with the youngest patient being 19 years old and the oldest being 91 years old. The frequency between genders was higher among men (52.21%) when compared to women (47.79%). Regarding the length of stay, the average was 27.24 days, with a minimum of 4 days and a maximum of 169 days. In the ICU the average was 21.11 days, with a minimum of 1 day and a maximum of 105 days.

There was a greater number of VAP (230 cases), followed by the presence of CAUTI (160 cases), CABSI with 103 cases, tracheobronchitis with 65 cases, NCAUTI with 33 cases, PNM with 14 cases and NCABSI with 9 cases (2.32%) (Graph 1). It should be emphasized that many patients had more than one HAI during the hospitalization period in several sites of infection. In addition to these, four of the analyzed patients (1%) also had *Clostridium difficile* infection during their hospital stay.

Graph 1 - Frequency of infections.



*CAUTI= catheter-associated urinary tract infection; NCAUTI= non-catheter-associated urinary tract infection; VAP= ventilator-associated pneumonia; PNM= pneumonia not associated with mechanical ventilation; CABSI= catheter-associated bloodstream infection; NCABSI= non-catheter-associated bloodstream infection. **Frequency expressed in number of patients (n) in the total analyzed sample. Source: Authors.

In regards to bacterial infections of the urinary tract (Table 1), it should be noted that most of them were caused by *Enterococcus faecalis*, representing 30 CAUTI (21.74%) and 11 NCAUTI (7.97%). Still, with a large percentage, there is *Klebsiella pneumoniae* carbapenemase (KPC), showing a high rate of infections by microorganisms with microbial resistance, represented by 20 patients in CAUTI and 8 in NCAUTI. Also, with high incidence rates, *Klebsiella pneumoniae* with extended spectrum beta-lactamase (ESBL) appears, which represented a total of 11 patients with CAUTI, while in NCAUTI, there was 1 case. In NCAUTI, there were also 2 cases of *Enterobacter cloacae* ESBL. Still, with a high percentage in CAUTI, there was *Escherichia coli* (11 patients) and multiresistant *Acinetobacter baumannii* (9 patients). The average time of use of the indwelling urinary catheter, which has an important relationship with CAUTI, was 15.45 days, with a maximum of 163 days of use.

Table 1 - Distribution of the number of bacterial urinary tract infections.

Microorganism	CAUTI (n)	NCAUTI (n)
Enterococcus faecalis	30	11
Klebsiella pneumoniae KPC	20	8
Escherichia coli	11	0
Klebsiella pneumoniae ESBL	11	1
Acinetobacter baumannii multirresistente	9	1
Enterococcus faecium	3	1
Burkholderia cepacea	2	0
Enterobacter cloacae	2	1
Klebsiella aerogenes	2	2
Klebsiella pneumoniae sensível	2	0
Enterobacter cloacae ESBL	1	2
Klebsiella oxytoca ESBL	1	0
Pseudomonas aeruginosa	1	1
Staphylococcus coagulase negativa	1	0
Acinetobacter baumannii sensível	0	1
MSSA	0	1

*CAUTI= catheter-associated urinary tract infection; NCAUTI= non-catheter-associated urinary tract infection. **Distribution expressed in number of patients (n) in the total analyzed sample. Source: Authors.

However, with an even higher percentage than bacterial infections, there are fungal infections in the urinary tract (Table 2), represented by 33 patients who had CAUTI by *Candida albicans* (23.91%), in NCAUTI there were 5 patients. Also, there have been cases involving *Trichosporum asahei*, *Candida glabrata, Candida tropicalis* and *Candida krusei*.

Table 2 - Distribution of the number of fungal urinary tract infections.

Microrganismo	CAUTI (n)	NCAUTI (n)
Candida albicans	33	5
Trichosporum asahei	5	0
Candida tropicalis	2	0
Candida glabrata	1	2
Candida krusei	1	0

*CAUTI= catheter-associated urinary tract infection; NCAUTI= non-catheter-associated urinary tract infection. **Distribution expressed in number of patients (n) in the total analyzed sample. Source: Authors.

Regarding bloodstream infections (Table 3), specifically CABSI there was a large number of Methicillin-sensitive *Staphylococcus aureus* (MSSA) (17 cases), followed by 16 cases of coagulase-negative *Staphylococcus sp.*, 14 multidrug-resistant *Acinetobacter baumannii*, 14 *Klebsiella pneumoniae* KPC, 12 *Enterococcus faecalis*, 10 *Klebsiella pneumoniae* ESBL. When not associated with a central venous catheter, NCABSI, the highest number (2 cases) involved the multidrug-resistant *Acinetobacter baumannii*. As the highest number of infections is related to the presence of the central venous catheter, the average days of use was 15.45 days, with a maximum of 163 days. In addition to the presence of the central catheter, 41.91% of the patients also used invasive blood pressure (IBP), which may also be related to the high number of IPCS.

Table 3 - Distribution of the number of bacterial blood stream infections.

Microorganism	CABSI (n)	NCABSI (n)
MSSA	17	1
Staphylococcus coagulase negativos	16	1
Acinetobacter baumannii multirresistente	14	2
Klebsiella pneumoniae KPC	14	0
Enterococcus faecalis	12	1
Klebsiella pneumoniae ESBL	10	1
Burkholderia cepacea	4	0
Escherichia coli	2	1
Klebsiella aerogenes	2	0
Klebsiella pneumoniae sensível	2	0
Streptococcus agalactiae	2	0
Acinetobacter baumannii sensível	1	0
Bacilus circulans	1	0
Corynebacterium striatum	1	0
Corynebacterium urealyticum	1	0
Enterobacter cloacae ESBL	1	0
Enterococcus faecium	1	0
MRSA	1	0
Proteus mirabilis	1	0
Pseudomonas aeruginosa	1	1
Serratia marcenses	1	0
Staphylococcus schleiferi	1	0
Streptococcus pneumoniae	1	0
Negative culture	2	1

*CABSI= catheter-associated bloodstream infection; NCABSI= non-catheter-associated bloodstream infection. **Distribution expressed in number of patients (n) in the total analyzed sample. Source: Authors.

There were also cases of fungal infections in the bloodstream (Table 4), all involving the use of a central venous catheter, most of which were caused by *Candida albicans*. Still, there were cases of *Candida tropicalis*, *Candida spp*. and *Rhodotorula glutinis*.

Most infections were related to the respiratory tract, with emphasis on VAP. Thus, the average number of days on mechanical ventilation is evident, as it contributes to increasing the risk of infection. The average was 21.15 days, with a maximum of 123 days of mechanical ventilation, which includes orotracheal intubation and tracheostomy. The performance of tracheostomy generally occurred after 20 days with orotracheal intubation, with an average of 7.1 days, with a maximum time of use of 108 days.

Table 4 - Distribution of the number of fungal blood stream infections.

Microorganism	CABSI (n)	NCABSI (n)
Candida albicans	8	0
Candida spp.	1	0
Candida tropicalis	1	0
Rhodotorula glutinis	1	0

*CABSI= catheter-associated bloodstream infection; NCABSI= non-catheter-associated bloodstream infection. **Distribution expressed in number of patients (n) in the total analyzed sample. Source: Authors.

Within the distribution of infections, the vast majority (112 cases) were represented by the multidrug-resistant *Acinetobacter baumannii*, evidencing the importance of this microorganism. It, in addition to encompassing a large number of VAP, covered a large number of cases of CAUTI (9), NCAUTI (1), CABSI (14), NCABSI (2), PNM (5) and tracheobronchitis (17). In addition to multidrug-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* also comprised many cases (39) of VAP, along with MSSA (37), Klebsiella pneumoniae KPC (25), Klebsiella pneumoniae ESBL (15), Stenotrophomonas maltophilia (13), Methicillin-resistant *Staphylococcus aureus* (MRSA) (10), susceptible *Klebsiella pneumoniae* (9), *Enterobacter cloacae* (7), *Serratia marcenses* (7) and *Escherichia coli* (6). In regards to PNM and tracheobronchitis, most infections also involved multidrug-resistant *Acinetobacter baumannii*. In the PNM there was also infection by *Pseudomonas aeruginosa* (3) and MSSA (3). Meanwhile, in tracheobronchitis, MSSA (10), *Pseudomonas aeruginosa* (9), *Burkholderia cepacea* (7), *Klebsiella pneumoniae* KPC (4) and *Stenotrophomonas maltophilia* (4) stood out. Furthermore, a high distribution of negative cultures can be observed, 20 within VAP and 6 in tracheobronchitis, and also no cultures, in 5 VAP, 3 PNM and 7 tracheobronchitis (Table 5).

Table 5 - Distribution of the number of bacterial airway infections.

Microorganism	VAP (n)	PNM (n)	Tracheobronchitis (n)
Multiresistant *Acinetobacter baumannii*	112	5	17
Pseudomonas aeruginosa	39	3	9
MSSA	37	3	10
Klebsiella pneumoniae KPC	25	0	4
Klebsiella pneumoniae ESBL	15	1	1
Stenotrophomonas maltophilia	13	1	4
MRSA	10	0	1
Susceptible *Klebsiella pneumoniae*	9	0	0
Enterobacter cloacae	7	0	3
Serratia marcenses	7	0	1
Escherichia coli	6	0	2
Burkholderia cepacea	4	0	7
Klebsiella aerogenes	4	0	0
Susceptible *Acinetobacter baumannii*	2	0	1
Corynebacterium striatum	2	0	0
Klebsiella oxytoca ESBL	2	0	0
Carbapenem-resistant *Pseudomonas aeruginosa*	2	0	0
Complex *Burkholderia cepacea*	1	0	0
Enterobacter aglomerans	1	0	0
Enterococcus faecium	1	0	0
Streptococcus pneumoniae	1	0	0
Citrobacter koseri	0	0	1
Enterobacter cloacae ESBL	0	0	0
Negative culture	20	0	6
No culture	5	3	7

*VAP= ventilator-associated pneumonia; PNM= pneumonia not associated with mechanical ventilation. **Distribution expressed in number of patients (n) in the total analyzed sample. Source: Authors.

Despite their lower expressiveness in airway infections, there was also the occurrence of fungal infections (Table 6). In VAP, there were cases of *Aspergillus sp.* (6 cases), *Candida tropicalis* (2 cases) and *Trichosporum asahei* (1 case). In tracheobronchitis, data showed 5 infections by *Candida albicans*, 2 by *Candida glabrata* and 2 by *Aspergillus sp*.

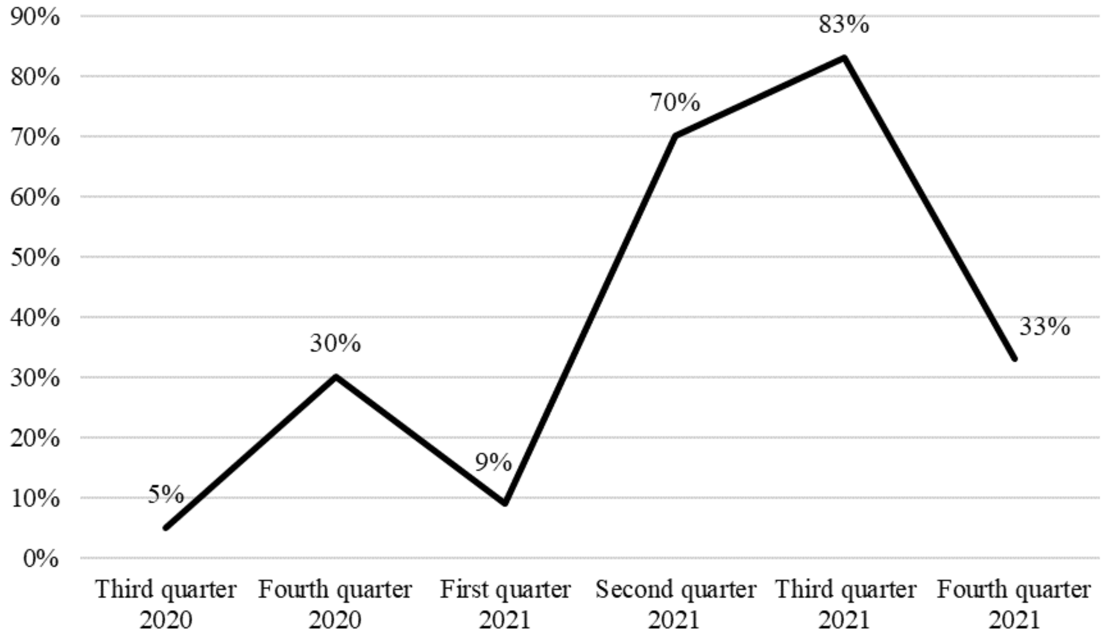
Table 6 - Distribution of the number of fungal airway infections.

Microorganism	VAP (n)	PNM (n)	Tracheobronchitis (n)
Aspergillus sp.	6	0	2
Candida tropicalis	2	0	0
Trichosporum asahei	1	0	0
Candida albicans	0	0	5
Candida glabrata	0	0	2

*VAP= ventilator-associated pneumonia; PNM= pneumonia not associated with mechanical ventilation. **Distribution expressed in number of patients (n) in the total analyzed sample. Source: Authors.

There was a large number of infections related to the multidrug-resistant *Acinetobacter baumannii*, showing the importance of this microorganism in all sites of infection and also highlighting it as a hospital concern. In the analyzed period, regarding the site of infection with the highest prevalence, VAP, there was an increase in infections from the first quarter of 2021, growing until reaching a peak in the third quarter of 2021, in which 83% of all VAP were caused by this microorganism. In the fourth quarter of 2021, there was a drop, however this data can only be confirmed with the analysis of the months of November and December, since the analysis was carried out only until the month of October (Graph 2).

Graph 2 - Distribution of ventilator-associated pneumonias caused by multidrug-resistant *Acinetobacter baumannii*



*Distribution expressed as a percentage (%) of VAP caused by multidrug-resistant *Acinetobacter baumannii* in relation to the total number of VAP in the analyzed periods. Source: Authors.

Also, when it comes to infections of the lower airways, the high degree of pulmonary involvement found in the patients can be highlighted, based on chest computed tomography. The majority 60.1%, corresponding to 245 patients, had an impairment of >50%, emphasizing the severity of the infection of the patients in the study. The other 25% (102 patients) had a pulmonary involvement from 25 to 50%, while 4.9% (20 patients) had an impairment of less than 25%. Also, 10.1% (41 patients) had an unspecified degree of impairment (Graph 3).

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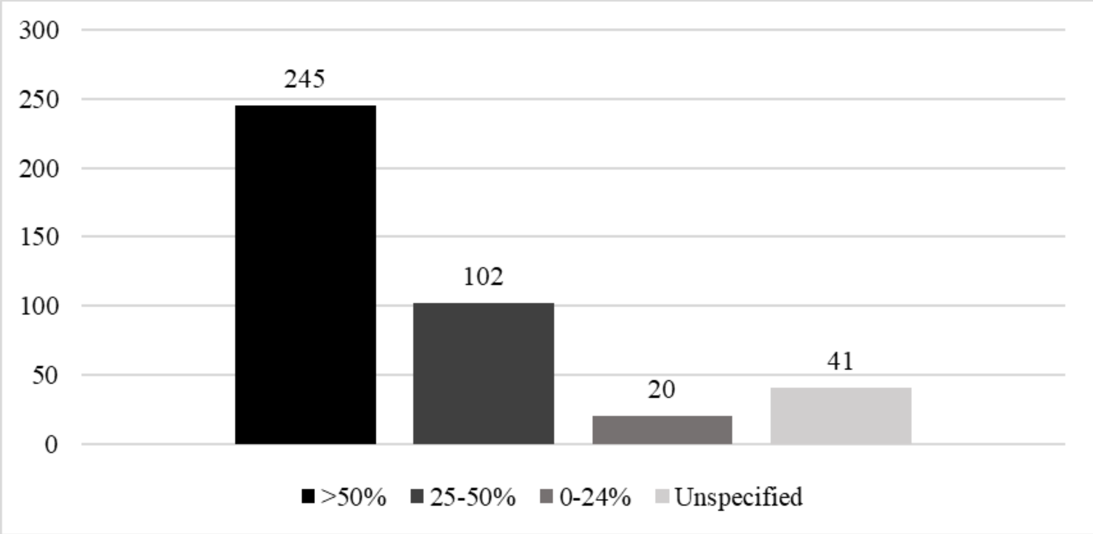
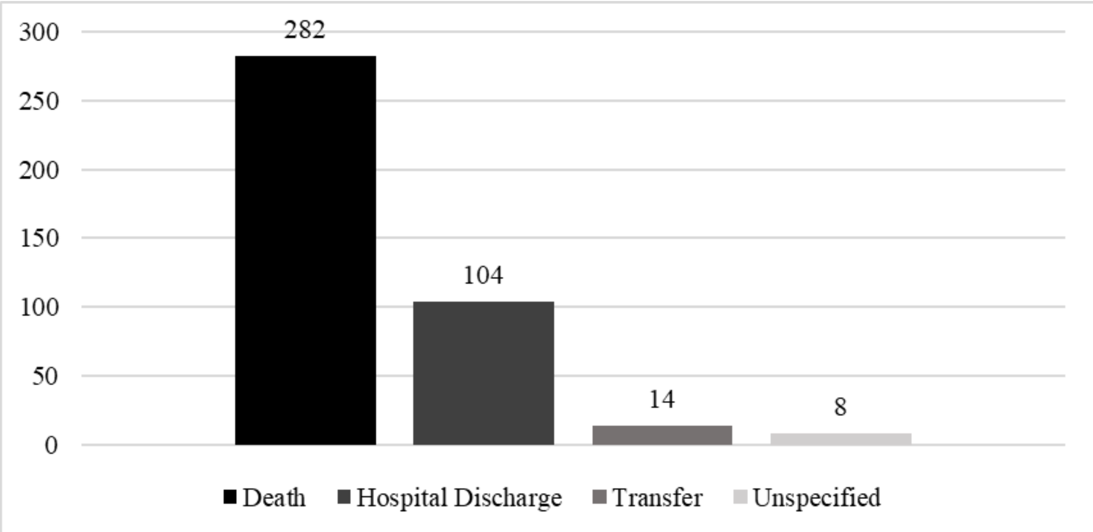
Graph 3 - Degree of lung impairment of patients.



*Frequency expressed in number of patients (n) of the total analyzed sample. Source: Authors.

Regarding the outcome of the patients (Graph 4), the majority (69.1%, 282 patients) died, indicating the severity of the conditions. Only 104 patients (25.5%) were discharged, 14 patients were transferred from the institution (3.4%) and 8 patients (2%) had no specified outcomes in the electronic medical record.

Graph 4 - Outcome of patients.



*Frequency expressed in number of patients (n) of the total analyzed sample. Source: Authors.

The main comorbidities found in the patients were systemic arterial hypertension in 53.7% of the patients, obesity in 66.4%, divided into overweight, obesity grades I, II and III based on the body mass index (BMI) and without specifying degree and also diabetes mellitus types 1 and 2, with 28.2%. As the outcome may be mainly related to the presence or absence of comorbidities and risk factors, logistic regression was performed to determine whether any of the conditions was a predictor of increased mortality or prolonged ICU stay (≥20 days).

Paradoxically, pulmonary thromboembolism was statistically significant as a predictor of lower mortality (OR=0.47; p= 0.0167), but it was an important factor in determining prolonged ICU stays (OR= 2; p= 0.0208). Deep venous thrombosis also had a major impact on longer ICU stays (OR=4; p=0.0205). Acute renal failure, in turn, was the most impacting factor in terms of mortality, especially in individuals who required dialysis, with an OR of 4.45 (p=0.0002). Finally, pressure ulcers and diabetic foot also showed opposite behaviors, being comorbidities that were inversely related to mortality (OR= 0.37; p= 0.014), but which increased the length of stay in the therapy unit intensive (2.63; p=0.0144). Hyperthyroidism and pre-diabetes were not analyzed, as only 1 patient had each of them. For the remaining conditions, there were no statistically significant differences regarding mortality or longer ICU stays (Table 7).

Table 7 - Analysis of comorbidities as risk factors for mortality and prolonged hospital stay.

Comorbidity	n (%)	OR (p) Mortality	OR (p) ≥20 days of ICU stay
Smoking			
Active smoker or smoked in the last 10 years	43 (10,54%)	0,91 (0,8459)	0,99 (0,99)
No	365 (89,46%)		
Drinking			
Active drinker or drinked in the last 10 years	14 (3,43%)	1,35 (0,6664)	0,58 (0,4210)
No	394 (96,57%)		
Obesity			
No	63 (15,4%)	Obesity grades II and III 0,8449 (0,4415)	Obesity grades II and III 0,99 (0,9623)
Overweight	113 (27,7%)		
Obesity grade I	75 (18,4%)		
Obesity grade II	42 (10,3%)		
Obesity grade III	30 (7,4%)		
Obesity, non-specified grade	11 (2,7%)		
Not evaluated	73 (17,9%)		
Malnutrition	1 (0,3%)		
Diabetes mellitus			
Yes	115 (28,2%)	0,0011 (0,9919)	0,0028 (0,655)
No	293 (71,8%)		
Systemic arterial hypertension			
Yes	219 (53,7%)	0,86 (0,5907)	0,9654 (0,8853)
No	189 (46,3%)		
Dyslipidemia			
Yes	56 (13,7%)	1,12 (0,6865)	0,66 (0,1785)
No	352 (86,3%)		
Pulmonary thromboembolism			
Yes	66 (16,2%)	0,47 (0,0167*)	2 (0,0208*)
Unconfirmed suspicion	15 (3,7%)		
No	327 (80,2%)		
Deep vein thrombosis			
Yes	17 (4,2%)	0,69 (0,42)	4 (0,0205*)
Unconfirmed suspicion	1 (0,2%)		
No	390 (95,6%)		
Chronic kidney disease			
Yes	3 (0,7%)	0,34 (0,073)	0,3 (0,0605)
No	405 (99,3%)		
Dialytic acute renal failure			
Yes	73 (17,9%)	4,45 (0,0002*)	1,09 (0,7716)
No	335 (82,11%)		
Non-dialytic acute renal failure			
Yes	142 (34,8%)	1,99 (0,0126*)	0,93 (0,7965)
No	266 (65,2%)		
Cardiopathy			
Yes	63 (15,4%)	1,54 (0,2614)	1,65 (0,1169)
No	345 (84,6%)		
Hepatopathy			
Yes	7 (1,7%)	1,41 (0,502)	0,45 (0,2562)
No	401 (98,3%)		
Hypothyroidism		1,39 (0,4363)	1,49 (0,3149)
Yes	38 (9,3%)		

No	370 (90,7%)		
Asthma/ bronchitis			
Yes	21 (5,2%)	0,73 (0,5527)	1,38 (0,5179)
No	387 (94,9%)		
Obstructive sleep apnea syndrome			
Yes	3 (0,7%)	1,39 (0,98)	1,88 (0,6328)
No	405 (99,3%)		
Pressure ulcer/diabetic foot			
Yes	39 (9,6%)	0,37 (0,014*)	2,63 (0,0144*)
No	369 (90,4%)		
Benign prostate hyperplasia			
Yes	11 (2,7%)	2,001 (0,4418)	2,93 (0,1499)
No	397 (97,3%)		
Cancer			
Yes	10 (2,5%)	2,98 (0,3184)	4,61 (0,0699)
No	398 (97,8%)		
Psychiatric disorders			
Yes	48 (11,79%)	0,69 (0,3183)	1,63 (0,1642)
No	359 (88,21%)		
Neurologic disorders			
Yes	33 (8,11%)	2,01 (0,18)	1,32 (0,5199)
No	374 (91,89%)		
Immunosuppression			
Yes	5 (1,23%)	4,01 (0,2630)	0,19 (0,1640)
No	402 (98,7%)		
Disability			
Yes	7 (1,7%)	5,35 (0,9688)	2,5 (0,4228)
No	401 (98,3%)		
Pregnancy / postpartum			
Yes	5 (1,3%)	0 (0,9744)	0,87 (0,89)
No	403 (98,8%)		

*Statistically significant p values. **Frequency expressed in number of patients (n) and percentage (%) of the total analyzed sample. Source: Authors.

When comparing each type of nosocomial infection with the same variables of the previous table, it was possible to notice that patients with pneumonia had lower mortality rates (OR= 0.31; p= 0.034), as well as patients with tracheobronchitis had less time hospitalization than patients with other types of infection (OR= 0.46; P=0.009). However, those who had VAP showed highly significant results in the increase in ICU length of stay, with an OR of 3.02 and p= 0.0000007) (Table 8).

Table 8 - Analysis of infections with mortality and length of stay.

Infection	OR (p) Mortality	OR (p) ≥20 days of ICU stay
CAUTI	1,28 (0,2719)	1,34 (0,1857)
NCAUTI	0,57 (0,1656)	1,23 (0,5881)
CABSI	1,3 (0,3317)	1,13 (0,6535)
NCABSI	3,6 (0,2857)	0,56 (0,5103)
Tracheobronchitis	0,62 (0,1038)	0,46 (0,009*)
PNM	0,31 (0,034*)	1,19 (0,7893)
VAP	1,05 (0,8161)	3,02 (0,0000007*)

*Statistically significant p values. **CAUTI= catheter-associated urinary tract infection; NCAUTI= non-catheter-associated urinary tract infection; VAP= ventilator-associated pneumonia; PNM= pneumonia not associated with mechanical ventilation; CABSI= catheter-associated bloodstream infection; NCABSI= non-catheter-associated bloodstream infection. Source: the authors.

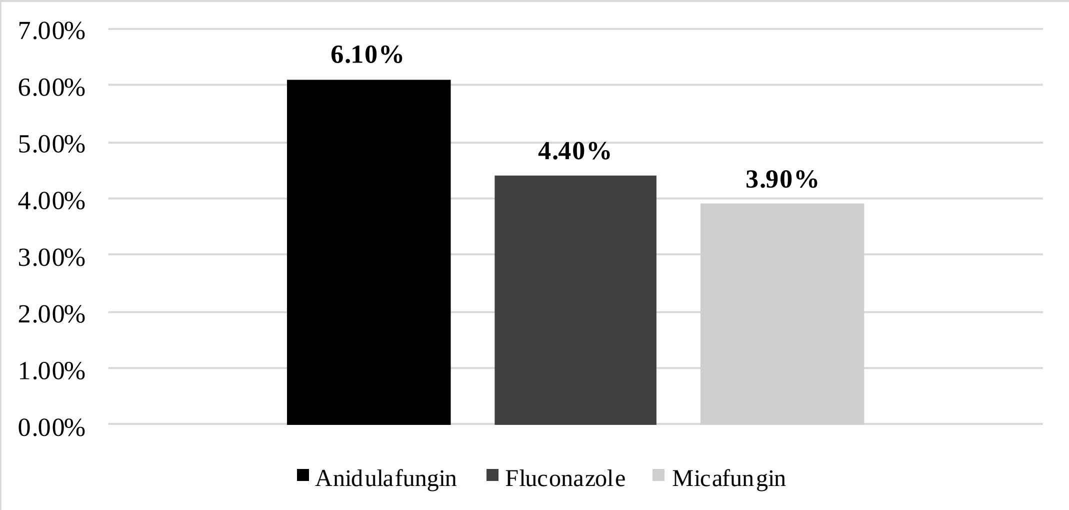
The frequency of antimicrobial use was also analyzed (Table 9). Thus, a large number of patients who used Piperacillin/tazobactam (88.2%), followed by Meropenem (76.7%), Ceftriaxone (50%), Azithromycin (47.1%) and Amikacin (38 .5%). There was also an expressive use of antifungals since, as already shown, there was an abundant number of fungal infections. Overall, they were used in 56 patients (13.73%). The vast majority used Anidulafungin, a total of 25 patients (6.1%), there was also use of Fluconazole, 18 patients (4.4%) and Micafungin, 16 patients (3.9%) (Graph 5). In addition to the use of antimicrobials and antifungals, there are many patients using in-hospital corticosteroid therapy, 389 patients (95.34%). The use of Ivermectin was still evident, 156 patients (38.33%) and Oseltamivir, 20 patients (4.9%).

Table 9 - Frequency of antimicrobial use.

Antimicrobial	n	%
Amikacin	157	38,5%
Amoxicillin + Clavulanate	3	0,7%
Ampicillin	22	5,4%
Ampicillin + Sulbactam	75	18,4%
Azithromycin	192	47,1%
Cefepime	17	4,2%
Ceftazidime	12	2,9%
Ceftazidime + Avibactam	9	2,2%
Ceftriaxone	204	50,0%
Ciprofloxacin	41	10,1%
Clindamycina	14	3,4%
Gentamicin	8	2,0%
Levofloxacin	47	11,5%
Linezolid	9	2,2%
Meropenem	313	76,7%
Metronidazole	8	2,0%
Oxacillin	48	11,8%
Piperacillin + Tazobactam	360	88,2%
Polymyxin B	75	18,4%
Sulfamethoxazole + Trimethoprim	21	5,2%
Teicoplanin	4	1,0%
Tigecycline	2	0,5%
Vancomycin	89	21,8%

*Frequency expressed in number of patients (n) and percentage (%) of the total analyzed sample. Source: Authors.

Graph 5 - Frequency of antifungal use.



*Frequency expressed as a percentage (%) of patients in the total analyzed sample. Source: Authors.

4. Discussion

Several bacterial infections occurred in the analyzed sample of patients with severe COVID-19, defined by the need for ICU care. It is pointed out that SARS-CoV-2 infection affected bacterial HAIs in several ways. The presence of an inflammatory condition induced by the primary infection, associated with structural damage caused by viral pneumonia and increased colonization by bacteria, usually multidrug-resistant, influences the acquisition of secondary infections in COVID-19. From this, there is a tendency for the rate of bacterial infection to be higher in critically ill COVID-19 patients (Nedel et al., 2022).

Worldwide, the main microorganisms related to HAI are the so-called ESKAPE pathogens: *Enterococcus faecium*, *Staphylococcus aureus, Klebisiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* species (Rice, 2008). A systematic review with meta-analysis developed from November 2019 to June 2021 (Kariyawasam et al., 2022) portrays that, in the COVID-19 pandemic, there are higher rates of infections and of a more resistant nature, especially in patients who were ventilated for long periods or in those hospitalized in ICUs. Risk factors include overall health, socioeconomic status, previous use of antibiotics and length of stay in a hospital environment. Thus, prior identification of patients at higher risk for these infections by multidrug-resistant microorganisms may improve prognosis and overall outcomes (Kariyawasam et al., 2022). In the present study, although patients with pneumonia had lower mortality rates (OR= 0.31; p= 0.034), this significantly increased the number of days spent in the ICU (OR= 3.02; p= 0.0000007).

In a study carried out in Lombardy, Italy, with 36 COVID-19 ICUs, it was shown that 774 adult patients with pneumonia had confirmed HAIs during their stay in the ICU. In that same study, 50% of the patients had VAP, in addition to 34% of the patients who were diagnosed with BSI, both being the most frequent HAIs (Grasselli et al., 2021). Based on that the highest percentage of VAP is highlighted, which was also observed in the present study. What differed was in relation to the second most common infection, which were UTI in the present study. Also, in a study designed with 148 hospitals, also referring to the presence of HAIs, it was shown that as the viral load of COVID-19 increased, there was a significant increase in CABSI and CAUTI (Baker et al., 2022).

In our study, the highest prevalence found were airway infections caused by the multidrug-resistant *Acinetobacter baumannii*, with 112 cases in VAP, 5 in PNM and 17 in tracheobronchitis, there were also cases involving susceptible *Acinetobacter baumannii*, with 2 cases of VAP and 1 of tracheobronchitis. In addition to the presence of airway infections, it also included cases of CABSI (16 multidrug-resistant and 1 susceptible) and UTI (10 multidrug-resistant and 1 susceptible). In a study carried out with 147 ICU patients with *Acinetobacter baumannii* infection, 32 of which also had COVID-19, confirms that bacterial superinfections can complicate the clinical course of patients with COVID-19 and identifies that serum lactate levels (>2mmol/l) in the time of infection, *Acinetobacter baumannii* colonization, development of bloodstream infection, and steroid therapy are important factors associated with multidrug-resistant *Acinetobacter baumannii* infection, associated with higher 30-day mortality rate (Russo et al., 2021). From this, the percentage of 69.1% of the patients in the studied sample that evolved to death (282 patients) and 25.5% (104 patients) who were discharged stands out.

An outbreak of carbapenemase-resistant *Acinetobacter baumannii reported* in patients with COVID-19 at the Hasharon Hospital in Israel (Gottesman et al., 2021) has been observed, as well as superinfections in patients in studies carried out in Spain, Mexico and Brazil (Durán-Manuel et al., 2021; Nebreda-Mayoral et al., 2022; Shinorara et al., 2021). In a study conducted in Bologna, Italy, the increase in the incidence of *Acinetobacter baumannii* infections in the ICU was highlighted, with an increase from 5.1 per 10,000 patients-day in January to April 2019 to 26.4 per 10,000 patients-day in January to April 2020 (O'Toole, 2021; Pascale et al., 2022). In the present study, there was a significant increase in infections in the analyzed period, with the peak of cases caused by multidrug-resistant *Acinetobacter baumannii* in the third quarter of 2021, with 83%.

In addition to *Acinetobacter baumannii* in airway infections, there was also a high number of cases of VAP involving *Klebsiella pneumoniae* (49 cases, 25 KPC, 15 ESBL and 9 susceptible), *Staphylococcus aureus* (47 cases, 37 MSSA and 10 MRSA), *Pseudomonas aeruginosa* (41 cases, 39 susceptible and 2 resistant to carbapenems), highlighting VAP as the highest number of infections (230 cases). Studies point to a higher rate of infections in the later stages of SARS-CoV-2 infection, due to the long period of mechanical ventilation. VAP ranges from 21 to 64% of patients requiring invasive mechanical ventilation (Flumagalli et al., 2022) and has a higher risk (hazard ratio 1.7 to 2) in COVID-19 patients compared to those without COVID-19, even in compared to those with severe influenza infection (Rouzé et al., 2021; Maes et al., 2021).

Aspegillus species often cause life-threatening airway infections, particularly in groups with risk factors such as the immunocompromised, transplant recipients, hematopoietic malignancies and severe COVID-19 even in the absence of immunosuppressive drugs (Song et al., 2020). The present study only includes patients with severe COVID-19; thus, the risk of aspergillosis is higher. Despite this, *Aspergillus sp*. was observed in 6 patients with VAP and 2 with tracheobronchitis. Fungi were predominant in the urinary tract, with different species of *Candida sp*., the highest number being *Candida albicans*, with 33 cases of CAUTI and 5 NCAUTI, but there were also cases of *Candida glabrata* (1 CAUTI and 2 NCAUTI), *Candida tropicalis* (2 CAUTI) and *Candida krusei* (1 CAUTI), and non-specified *Candida sp*. among the CABSI, with 10 cases.

The pattern of pathogens found in the urinary tract showed some divergence from studies in the literature, such as a study conducted with 989 patients in Barcelona, Spain, in which most ICUs were caused by *Escherichia coli*, *Klebsiella pneumoniae* and *Enterococcus faecium* (Garcel-Vidal et al., 2021; O'Toole, 2021). Whereas, most of the infections observed in the present study were by *Enterococcus faecalis* (30 CAUTI and 11 NCAUTI), *Klebsiella pneumoniae* (CAUTI: 20 KPC, 11 ESBL and 2 sensitive; NCAUTI: 8 KPC and 1 ESBL) and *Escherichia coli* (11 CAUTI).

Primary bloodstream infections have a high incidence and are more frequent in patients with COVID-19 (Buetti et al., 2021). In the present study, the presence of the central catheter was the mostly associated, being in third place (103 cases) behind VAP (230 cases) and CAUTI (160 cases), other studies presented it as the second most frequent infection (Grasseli et al., 2021; Russel et al., 2021). In the analyzed sample, CABSI were caused mainly by *Klebiella pneumoniae*, with 26 cases (14 KPC, 10 ESBL and 2 susceptible), *Staphylococcus aureus*, with 18 cases (17 MSSA and 1 MRSA), in addition to 16 cases involving the Coagulase-negative *Staphylococcus* and 15 *Acinetobacter baumannii* (14 multiresistant and 1 susceptible).

In-hospital corticosteroid therapy was predominant in our study (95.34%), the literature indicates that the use of dexamethasone for 28 days resulted in lower mortality, especially in those on invasive mechanical ventilation (Welte et al., 2021; Ko et al., 2021). In the present study, hospitalization lasted an average of 27.24 days (minimum of 4 days and maximum of 169 days), with an average of 21.11 days in the ICU (minimum of 1 day and maximum of 105 days) and in use of invasive mechanical ventilation for an average of 21.15 days (maximum of 123 days). From this, the use of corticotherapy may have been evidenced as an ally in many cases. However, the literature points out that the prolonged use of high doses of steroids may be associated with the immunomodulatory effects of these drugs, which may make patients prone to superinfections (Tomazini et al., 2020).

It is worth mentioning that in our research, in addition to empirical therapy, a large number of patients were already receiving broad-spectrum antibiotic therapy before entering the ICU. This data was also observed in another study with 68% of patients. In a review performed by Rawson et al. in 2020, revealed that 72% of patients diagnosed with SARS-COV-2 received empirically prescribed broad-spectrum antimicrobial therapy in critical and non-critical settings (Rawson et al., 2020). While the meta-analysis by Langford et al. (2020) with 3338 hospitalized and critical COVID-19 patients showed that the majority received antibiotics (71.9%), although the rates of bacterial co-infection and secondary infection in these patients were only 3.5% and 14.3%, respectively (Langford et al., 2020).

It is evident that the choice of antimicrobial therapy is made based on the epidemiology of the hospital institution and correlation with the patient's risk factor. When there is no presence of bacterial infection, it should be discontinued early (Langford et al., 2020). In the institution under study, there was a predominance of the use of Piperacillin/Tazobactam in 360 patients (88.2%), Meropenem in 313 (76.7%), Ceftriaxone in 204 (50%), Azithromycin in 192 (47.1%) and Amikacin in 157 (38.5%). It is worth noting that a large number of patients in the sample were hospitalized having already completed the Azithromycin regimen, and it was not possible to analyze that data. In addition to the use of antibiotics, there was use of antifungals such as Anidulafungin (6.1%), Fluconazole (4.4%) and Micafungin (3.9%). Another study [34], also addressing patients with severe COVID-19 (79 patients), the main antimicrobials used were ceftriaxone (90.7%), vancomycin (86%), polymyxin B (74.4%), azithromycin (69.8% and meropenem (67.4%), evidencing the vast use of broad-spectrum antibiotics. Also, Micafungin was used in 22.2% and Fluconazole in 11.1% (Singulani et al., 2022).

Studies indicate that obesity is a risk factor for hospitalization due to COVID-19, in addition to it being a risk factor for the development of severe COVID-19 (Docherty et al., 2020). The present study showed a percentage of 66.4% of overweight and obese patients. In England, a study involving 387,109 patients, in which 760 were hospitalized due to SARS-CoV-2, 176 (23.5%) were obese (Docherty et al., 2020). In which unhealthy behaviors such as physical inactivity, smoking, and obesity accounted for up to 51% of the population-attributable fraction of severe COVID-19. In addition, these patients were also associated with the need for oxygen, ICU and invasive mechanical ventilation, and also to having a reduced chance of extubating (Docherty et al., 2020; Richardson et al., 2020). Despite previous data on obesity in the present study, grade II and III obesity did not seem to have a significant impact on mortality (OR=0.8449; p=0.4415) and longer ICU stay (OR=0.99; p =0.9623). However, as a predictor of mortality, acute renal failure (OR= 4.45; p=0.0002) and deep venous thrombosis were associated with longer ICU stays (OR= 2; p= 0.0208). A systemic review with meta-analysis of 42 studies and 423,117 patients (Dessie & Zewotir, 2021) was consistent in affirming the contribution of gender, age, smoking, especially active smoking, obesity, acute kidney injury and D-dimer as risk factors to increase the need of advanced medical care. In addition to other factors such as cardiovascular disease, cancer, as they are associated with a risk for a fatal outcome associated with COVID-19 (Dessie & Zewotir, 2021).

The main limitations of our study are the fact that it was a single center, with only 408 patients, retrospectively performed over a period of nineteen months, involving the analysis of electronic medical records in a period of high hospital demand and shortage of professionals imposed by the COVID-19 pandemic. The sample included only patients in the ICU with secondary infections, that is, only HAIs, from which all co-infections and pathogens acquired in the community were excluded. There is also the impact related to data prior to the entry of a number of patients in the institution and transfers that occurred during hospitalization, which prevented the assessment of the outcome of these patients. The empirical therapy used may have had an impact, affecting the results of cultures, especially those with negative results. Other studies are needed to compare and clarify HAIs in patients diagnosed with COVID-19.

5. Conclusion

In conclusion, the high percentage of HAIs during hospitalization in the ICU of patients with COVID-19 was evidenced, with emphasis on VAP, followed by CAUTI and CABSI. The microorganism with the highest expression was the multidrug-resistant *Acinetobacter baumannii*, which had a significant increase in the analyzed period. Considerable cases of *Pseudomonas aeruginosa*, *Staphylococcus aureus, Klebsiella pneumoniae* and *Stenotrophomonas maltophilia* have occurred among VAP. Most CAUTI involved *Enterococcus faecalis, Klebsiella pneumoniae* and *Escherichia coli*, and the majority of CABSI were related to *Klebiella pneumoniae, Staphylococcus aureus*, coagulase-negative *Staphylococcus* and *Acinetobacter baumannii*. There was a considerable number of fungal infections, mainly in the urinary tract associated with *Candida albicans*. Patients with VAP had the lowest mortality rates, but this rate increased significantly the more the ICU days of stay. The most impactful predictor of mortality was acute renal failure and the one with the lowest mortality rate was pulmonary thromboembolism. There was a significant use of antimicrobials and antifungals, a high degree of pulmonary impairment and evolution to death. More studies are needed for comparison and analysis, as well as providing data to improve infection control and antimicrobial management practices in health care in order to reduce the occurrence of HAIs and antibiotic resistance. From the present study, it is suggested that similar research be applied in other hospitals on an ongoing basis, not only to define the impact COVID had on associated infections, but also to better establish the characterization of the microorganisms that cause the most impact in the hospital where they operate and to possibly be able to establish a correlation between the use of specific antibiotics and the emergence of new resistance, for example.

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