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Healthcare-Associated Infections in patients with Covid-19: Assessment of commorbidities and risk of mortality

Infecções Associadas à Saúde em pacientes com Covid-19: Avaliação de comorbidades e risco de mortalidade

Infecciones Asociadas a la Salud en pacientes con Covid-19: Evaluación de comorbilidades y riesgo de mortalidad

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Abstract
Healthcare-associated infections are a known factor that is especially difficult to control within healthcare institutions. They are responsible for increased mortality, as well as increased length of stay and costs. This is a retrospective observational cross-sectional study that aims to elucidate information about infections acquired in the hospital environment by patients with a confirmed diagnosis of COVID-19, who are more susceptible to this condition; it was conducted from March 2020 to March 2022 at a hospital in the southern region of Brazil. Data were collected from electronic medical records, and the profile of these infections was defined; the frequencies of the main comorbidities and main infections were analyzed, with site and etiological agent being discriminated, and the antimicrobials that were used being specified. The mortality rate of patients with obesity was 2.3 times higher, while that of pregnant and postpartum women was 11.3 times higher.
Keywords: Cross infection; COVID-19; Comorbidity.

Resumo
As infecções associadas aos cuidados de saúde são um fator conhecido que é especialmente difícil de controlar dentro das instituições de saúde. Elas são responsáveis por aumento da mortalidade, bem como por maior tempo de internação e custos. Este é um estudo observacional retrospectivo transversal que visa elucidar informações sobre infecções adquiridas no ambiente hospitalar por pacientes com diagnóstico confirmado de COVID-19, que são mais suscetíveis a essa condição; foi realizado de março de 2020 a março de 2022 em um hospital na região sul do Brasil. Os dados foram coletados a partir de prontuários eletrônicos, e o perfil dessas infecções foi definido; as frequências das principais comorbidades e das principais infecções foram analisadas, com o local e o agente etiológico sendo discriminados, e os antimicrobianos que foram utilizados sendo especificados. A taxa de mortalidade de pacientes com obesidade foi 2,3 vezes maior, enquanto a de gestantes e puérperas foi 11,3 vezes maior.
Palavras-chave: Infecção hospitalar; COVID-19; Comorbidade.

Resumen
Las infecciones asociadas a la asistencia sanitaria son un factor conocido que es especialmente difícil de controlar dentro de las instituciones de salud. Son responsables de un aumento de la mortalidad, así como de una mayor duración de la estancia y costos. Este es un estudio observacional retrospectivo transversal que tiene como objetivo elucidar información sobre infecciones adquiridas en el entorno hospitalario por pacientes con diagnóstico confirmado de COVID-19, quienes son más susceptibles a esta condición; se realizó desde marzo de 2020 hasta marzo de 2022 en un hospital de la región sur de Brasil. Los datos se recopilaron a partir de historias clínicas electrónicas, y se definió el perfil de estas infecciones; se analizaron las frecuencias de las principales comorbilidades y de las principales infecciones, con discriminación del sitio y del agente etiológico, y se especificaron los antimicrobianos que se utilizaron. La tasa de mortalidad de los pacientes con obesidad fue 2,3 veces mayor, mientras que la de mujeres embarazadas y en el posparto fue 11,3 veces mayor.
Palabras clave: Infección hospitalaria, COVID-19; Comorbilidad.

1. Introduction

Healthcare-Associated Infections (HAIs) have gained notoriety since the 1990s in Brazil, when the term was conceived as a way of encompassing infections occurring in any healthcare setting, not just in hospital environments (Araújo, Pereira, 2017). According to the Center for Disease Control and Prevention (CDC), an American health regulatory body, in order to be considered HAIs, these infections must be diagnosed from the third day of the patient's hospitalization (Centers for Disease Control and Prevention, 2023). HAIs have negative effects on morbidity, mortality, and healthcare costs (ANVISA, 2023). Speaking specifically about the economic burden generated by them, it is estimated that the annual cost in the United States of America ranges from 35.7 to 45 billion US dollars, and that in Europe it stands at 7 billion euros. Meanwhile, in Brazil, the estimated daily cost of a patient with HAI is 55% higher compared to a patient without HAI (ANVISA, 2023).

The COVID-19 pandemic has had a major impact on healthcare systems around the world. Baker et al. (2021) indicates that, during this period, there was a large increase in catheter-associated bloodstream and urinary tract infections, in addition to an increase in cases of bacteremia caused by several multidrug-resistant microorganisms of interest. Furthermore, due to this new reality, it was necessary to investigate the epidemiological profile of patients with COVID-19. In this context, there is a greater risk of disease severity for hypertensive patients, liver disease patients, patients with kidney injury, shock, severe acute respiratory syndrome, diabetes, and coronary artery disease (Khateri et al., 2020). Age also appears to be a relevant risk factor for mortality, with elderly patients being at a higher risk (Subramaniam et al., 2022).

A study conducted in Italian hospitals found that patients admitted with SARS-CoV-2 are at greater risk of developing HAIs, especially pneumonia related to mechanical ventilation, and bloodstream infections caused by multidrug-resistant microorganisms. These findings prolonged intubation time and increased mortality in these patients (Grasselli et al, 2021). The incidence of HAIs appears to increase according to the patients' length of hospital stay, especially when it is longer than 4 weeks (Butt et al., 2023).

This is a retrospective observational cross-sectional study that aims to elucidate information about infections acquired in the hospital environment by patients with a confirmed diagnosis of COVID-19, who are more susceptible to this condition; it

was conducted from March 2020 to March 2022 at a hospital in the southern region of Brazil.

2. Methodology

Study design

This is a retrospective observational cross-sectional study of quantitative nature (Pereira et al., 2018), using using means, standard deviations and statistics (Shitsuka et al., 2014; Vieira, 2021), in which the electronic medical records of patients admitted to the Intensive Care Unit (ICU) of a hospital in the southern region of Brazil were analyzed. The main objective was to find out which comorbidities would raise the mortality of patients admitted to intensive care with COVID-19 who acquired healthcare-associated infections (HAIs). The patients' electronic medical records were analyzed, covering the period from March 2020 to March 2022.

Sample size

The sample size calculation of 385 individuals was obtained considering a 95% confidence interval, with an allowable error of 5% and the smallest difference between the groups that is clinically relevant (50%) (Lauris, 2023). However, within the period studied, data on 407 patients were collected, excluding losses.

Inclusion criteria

Patients who were admitted to the hospital with COVID-19 and who had HAIs, confirmed by laboratory culture or equivalent report, were included in the study. Patients with HAIs who were diagnosed from the third day of their hospital stay and who were in the Intensive Care Unit were selected. The diagnosis of COVID-19 was confirmed by rapid test, serology, or RT-PCR (Reverse transcription polymerase chain reaction). For sample selection, the patients were not discriminated based on gender, age, or ethnicity.

Exclusion criteria

Those patients who presented infections before the third day of hospitalization, who did not have a confirmed diagnosis of COVID-19, or who were transferred, making it impossible to know the outcome, were excluded.

Data collection

Data were collected from electronic medical records and organized in a database to be later analyzed.

Statistical analysis

Data were statistically analyzed using the Jamovi 2.3.28® software. The frequencies (absolute and relative) were determined, and the data were subjected to chi-square statistical tests with continuity correction and Fisher's test, when applicable. The p value was considered statistically significant when lower than 0.05. This research followed the STROBE initiative for reporting observational studies (Von Elm et al.; STROBE Initiative, 2008). To be carried out, this project was previously approved by the Research Ethics Committee (COEP) under opinion number 5.503.719.

3. Results

During the period between March 2020 and March 2022, there were 422 notifications of patients with COVID-19 who presented HAIs. In total, 15 were transferred to other institutions and excluded from the study because there was no possibility

of knowing the outcome. Data on the remaining 407 patients were analyzed. Among these, 213 (52%) were men and 194 (48%) were women, with an average age of 57.3 years (±14.4).

Regarding the types of bacterial infections acquired during their hospital stay (Table 1), the most prevalent were airway infections (359), followed by urinary tract infections (202), and bloodstream infections (114).

The large number of cases of pneumonia associated with mechanical ventilation (VAP), as well as of catheter-associated urinary tract infections (UTI) and bloodstream infections is notable.

Table 1 – Frequency of HAIs in patients with COVID-19.

Types of infection		n (%)
Airway infections	**Total**	**359 (100)**
	Pneumonia associated with mechanical ventilation	264 (74)
	Tracheobronchitis	77 (21)
	Pneumonia	18 (5)
Urinary tract infections	**Total**	**202 (100)**
	Catheter-associated urinary tract infection	169 (84)
	Non-catheter-associated urinary tract infection	33 (16)
Bloodstream infections	**Total**	**114 (100)**
	Catheter-associated primary bloodstream infection	106 (93)
	Non-catheter-associated primary bloodstream infection	8 (7)

Source: Authors.

The frequencies of the etiological agents of infections were analyzed, given the interest in observing the resistance profile of these microorganisms in the region. Due to this fact, the main etiological agents were also discriminated according to their resistance to antibiotic therapy. There were 32 cultures with negative results, and, in 12 cases, there was no culture collection. The microorganisms most present in airway infections were Acinetobacter baumannii MR (multidrug-resistant), methicillin-sensitive Staphylococcus aureus (MSSA), and Pseudomonas aeruginosa. In urinary tract infections: Enterococcus faecalis, Candida albicans, and Klebsiella pneumoniae KPC. In bloodstream infections: MSSA, coagulase-negative Staphylococcus, and Acinetobacter baumannii MR. Their frequency and the frequency of other microorganisms are shown in Table 2.

Table 2 – Frequency of microorganisms by type of infection.

Microorganism	Total (%)	VAP (%)	PNM (%)	TCB (%)	CA/UTI (%)	NCA/UTI(%)	CA/PBSI (%)	NCA/PBSI (%)
Glucose-nonfermenting gram-negative bacilli	**289 (36)**	**185 (23)**	**10 (1)**	**43 (5)**	**22 (3)**	**3 (0)**	**24 (3)**	**2 (0)**
Acinetobacter baumannii MR	**170 (21)**	114	5	18	18	1	13	1
Pseudomonas aeruginosa	**61 (8)**	37	4	12	1	1	5	1
Burkholderia cepacia	**30 (4)**	16	0	6	3	0	5	0
Other glucose-nonfermenting gram-negative bacilli	**19 (2)**	14	1	4	0	0	0	0
Acinetobacter baumannii	**7 (1)**	2	0	3	0	1	1	0
Pseudomonas aeruginosa KPC	**2 (0)**	2	0	0	0	0	0	0
Enterobacteria	**227 (28)**	**87 (11)**	**1 (0)**	**17 (2)**	**74 (9)**	**16 (2)**	**30 (4)**	**2 (0)**
Klebsiella pneumoniae KPC	**78 (10)**	30	0	5	23	7	13	0
Other enterobacteria	**52 (7)**	24	0	7	13	4	4	0

Klebsiella pneumoniae ESBL	**47 (6)**	17	1	2	17	0	9	1
E. coli	**35 (4)**	8	0	2	17	5	2	1
Klebsiella pneumoniae	**15 (2)**	8	0	1	4	0	2	0
Gram-positive bacteria	**199 (25)**	**53 (7)**	**3 (0)**	**18 (2)**	**54 (7)**	**12 (2)**	**56 (7)**	**3 (0)**
MSSA	**74 (9)**	38	3	15	0	1	16	1
Enterococcus faecalis	**71 (9)**	0	0	0	48	10	12	1
Coagulase-negative *Staphylococcus*	**18 (2)**	0	0	0	1	0	16	1
MRSA	**15 (2)**	10	0	2	0	0	3	0
Other gram-positive cocci	**13 (2)**	2	0	0	5	1	5	0
Gram-positive bacilli	**8 (1)**	3	0	1	0	0	4	0
Fungi	**82 (10)**	**9 (1)**	**0**	**2 (0)**	**55 (7)**	**6 (1)**	**10 (1)**	**0**
Candida albicans	**55 (7)**	0	0	0	42	4	9	0
Other fungi	**27 (3)**	9	0	2	13	2	1	0

VAP – ventilator-associated pneumonia; PNM – pneumonia; TCB – tracheobronchitis; CA/UTI – catheter-associated urinary tract infection; NCA/UTI - non-catheter-associated urinary tract infection; CA/PBSI – catheter-associated primary bloodstream infection; NCA/PBSI – non-catheter-associated primary bloodstream infection; MR – multidrug resistant; MSSA – Methicillin-sensitive *Staphylococcus aureus*; MRSA – Methicillin-resistant *Staphylococcus aureus*; KPC - carbapenemase; ESBL – extended spectrum beta-lactamase. Source: Authors.

About the frequency of antimicrobial use in the study, meropenem, Penicillins, azithromycin and 3rd generation cephalosporins were used in up to 811 (72%) of 1128 antibiotic administration. The remaining 28% was divided among 10 other antimicrobials from different classes.

Finally, the analysis of the frequencies of the patients' comorbidities in the present study revealed that the 5 most prevalent were: obesity, diabetes mellitus, current or previous tobacco smoking, heart disease, and dyslipidemia. The frequencies of each comorbidity assessed in this study are described in Table 3.

Table 3 – Frequency of comorbidities and Odds Ratio (OR) among study patients

Comorbidity (n=407)	**OR**	**p-value**		**n (%)**
Obesity	2.30 (1.1 - 4.8)	0.034x	**Total**	**254 (62)**
			Overweight	110 (27)
			Obesity Class I	73 (18)
			Obesity Class II	41 (10)
			Obesity Class III	30 (7)
			Others	153 (38)
			Not assessed	80 (20)
			Obese, class not specified	12 (3)
			Malnutrition	1 (0)
			Not obese	60 (15)
Diabetes mellitus	0.76 (0.5 - 1.2)	0.343		**117 (29)**
Current or previous tobacco smoking	0.65 (0.4 - 1.1)	0.169		**92 (23)**
Heart disease	0.48 (0.2 - 0.9)	0.052		**67 (17)**
Dyslipidemia	0.73 (0.4 - 1.4)	0.465		**55 (14)**

Psychiatric illness	1.38 (0.7 - 2.7)	0.414		**49 (12)**
COPD	0.54 (0.2 - 1.5)	0.324		**29 (7)**
Neurological illness	0.46 (0.2 - 1.2)	0.171		**33 (8)**
Asthma/bronchitis	1.39 (0.5 - 3.5)	0.658		**21 (5)**
Chronic kidney disease	1.98 (0.7 - 5.3)	0.172		**17 (4)**
Cancer	0.29 (0.03 - 2.4)	0.301		**10 (3)**
Liver disease	1.10 (0.2 - 5.7)	1.000		**7 (2)**
Immunosuppression	0.68 (0.07 - 6.2)	1.000		**5 (1)**
Gestation	11.3 (1.25 - 102)	0.0200	**Total**	**5 (1)**
			Pregnant	1 (0)
			Postpartum woman	4 (1)
			No	402 (99)

COPD – chronic obstructive pulmonary disease.
[x] statistically significant p-value by the chi-square test with continuity correction.
[Φ] statistically significant p-value by Fisher's test.
Source: Authors.

The odds ratios and "p" values were analyzed to define mortality according to the presence of comorbidities (Table 3). The "p" values were calculated using the chi-square test with continuity correction and Fisher's exact test, when applicable. The "p" value was considered statistically significant when below 0.05. The "obesity" and "pregnancy" variables were grouped due to their small sample size when stratified. It was found that patients with obesity (overweight, obesity class I, II and III) were 2.3 more likely to pass away, and pregnant or postpartum patients were 11.3 more likely to pass away (however, this variable has a reduced sample number, n=5).

4. Discussion and Final Considerations

Our study observed that patients with COVID-19 and healthcare-associated infections (HAIs), and who had obesity and overweight as a risk factor, have a 2.3 higher risk of death. According to the Center for Disease Control and Prevention (CDC), an American health regulatory body, diabetes mellitus, current or previous tobacco smoking, heart disease, dyslipidemia, psychiatric illness, neurological illness, asthma, bronchitis, chronic kidney disease, cancer, liver disease, immunosuppression, pregnancy, and obesity are the main risk comorbidities for mortality in isolated COVID-19 (Centers for Disease Control and Prevention, 2023). A study published in the Journal of the American Medical Association (JAMA) also found that certain comorbidities, such as obesity, are risk factors for hospital admission due to COVID-19 (Richardson et al., 2020). Furthermore, obesity is also a risk factor for the development of severe cases of the disease, along with sex, age, tobacco smoking (especially active smoking), acute kidney injury, and D-dimer test results (Dessie, Zewotir, 2021). Additionally, it found that pregnant or postpartum women had 11.3 more chances, but this piece of data had a reduced n.

Moreover, the frequency of healthcare-associated infections was observed, especially pulmonary infections associated with mechanical ventilation. There was also a high prevalence of catheter-related urinary tract and bloodstream infections. This is consistent with what was observed in a study carried out with information on mortality from COVID-19 in Qatar, which reported an increase in bacterial infections with longer hospitalization time (Butt et al., 2023). Another article, based on data obtained from 148 American hospitals, showed an increase in bloodstream and urinary tract infections of more than 60% and 43%, respectively, for the expected period of 7 months (Baker et al, 2021). It is proven that the introduction of invasive devices such as mechanical ventilation and urinary and central catheters are known risk factors for the development of HAIs (ANVISA,

2023). As strategies to combat these infections, a better assessment of the period of time necessary for these devices to remain in each patient can be discussed.

Regarding the microorganisms that cause these pathologies, there is a prevalence of those with multi-resistant profiles such as Acinetobacter baumanii MR and Klebsiella pneumoniae KPC and ESBL, as well as fungal infections. This is a possible alarm signal for the healthcare system. Comparatively, an Italian multicenter study detected the presence of enterobacteria and MRSA as the main causes of ventilator-associated pneumonia (which differs from our study, in which there was a higher prevalence of Acinetobacter baumannii), while bloodstream infections presented gram-positive and gram-negative microorganisms in almost equal proportion, similar to what was observed in the present study (Grasselli et al., 2021). It is also important to note the high frequency of use of certain antimicrobials, especially meropenem, Penicillins, azithromycin, and 3rd generation cephalosporins, to the detriment of others. This may be due to the intrinsic resistance profile of the aforementioned bacteria, but it also brings attention to the development of bacteria that are multi-resistant to antimicrobials.

Obtaining data from a number of patients greater than the minimum required sample size can be considered a strength for data validation. Furthermore, the fact that the patients were admitted to an Intensive Care Unit allowed for greater observation and close attention by professionals from various fields to their health situation, in addition to reducing the potential heterogeneity of the sample.

Limiting factors of the study include the fact that the data were collected from electronic medical records, and therefore depend on information input by the professionals. As a measure to reduce the biasing effect, extensive research was carried out during the days of hospitalization with professionals from various areas. Furthermore, the study addresses the microbiological situation in the region where it was conducted, although similar reports have occurred in other locations. Therefore, it would be interesting for this study design to be applied in other centers, so that it is possible to define a profile of which patients are most at risk and even what preventive measures could be taken to minimize the risk of mortality.

5. Conclusion

Our study aims to shed light on comorbidities of importance for the mortality of patients with COVID-19 who develop HAIs during their hospital stay. Despite the high frequency of certain comorbidities, the main finding was the 2.3 times higher risk of mortality in patients with obesity and overweight. This result could lead to the creation of new protocols for these patients upon hospital admission, enabling a more attentive care and possibly a reduction in mortality, or even the development of a strategy to prevent complications from this risk factor. In order for this to be validated, it would be important to replicate this study design in other centers.

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Research ethics and patient consent

This study was approved by the Institutional Ethics Committee of the State University of Ponta Grossa (under opinion number 5.503.719). All procedures were in accordance with the 1964 Declaration of Helsinki and its later amendments, or with comparable ethical standards. The consent form for this retrospective and non-invasive study was not required by the local ethics committee. The latter allowed access to raw data in the hospital's electronic database.

Authorship statement

Conceptualization: G.A.F.R., B.K., A.C.F.M., G.A.J., E.G.M.; Resources: F.A.S., M.D.R.G, C.A.S.I., L.B.; Data Curation: G.A.F.R., F.A.S., E.G.M.; Writing-Original Draft Preparation: G.A.F.R.; Writing, Reviewing, and Editing: all authors; All authors meet the ICMJE authorship criteria.

Conflict of Interest

The authors declare that there were no conflicts of interest.

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