Haematological and biochemical parameters associated with *Candida* spp. infections in patients with severe Covid-19

Parâmetros hematológicos e bioquímicos associados com infecção por Candida spp. em pacientes com Covid-19 severa

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Abstract

Background: Healthcare-associated infections increase the risk of colonisation by multidrug-resistant microorganisms (MDR). Fungal infections are more prevalent in immunocompromised patients and carriers of underlying diseases. Covid-19 infection increased hospitalisation in intensive care units (ICU), which contributed to the increase in fungal co-infections and aggravated the morbidity and mortality of patients. **Objectives**: This study aimed to describe the occurrence of *Candida spp.* in patients with severe Covid-19 and to measure the association of risk factors for these co-infections. **Methods**: This article presents a retrospective cohort study conducted at a reference hospital in the state of Pernambuco. The medical records of 102 patients admitted to the ICU from June to August 2020, diagnosed with severe Covid-19 upon confirmation of the result by RT-PCR, were evaluated. The relationship between patients with fungal infections and the control group was observed by analysing the laboratory parameters. **Results**: Of the 102 patients evaluated, eight developed co-infections with *Candida spp.*. Among the eight cases, there were three deaths. Compared with a control group, patients co-infected with *Candida spp.* and Covid-19 had a higher number of total leukocytes, neutrophilia and higher plasma urea. **Conclusion**: Some biochemical and hematological changes were associated with the *Candida spp.* Infection. We did not detect resistance to the use of antifungal agents such as Fluconazole, Voriconazole, Caspofungin, Micafungin, Amphotericin B, and Fluocytosine. Relationship among *Acinetobacter baumannii* with two of the three deaths of individuals diagnosed with fungal infection, suggests an important morbidity of polymicrobial infections in patients with severe Covid-19.

Keywords: Covid-19. SARS-CoV-2. *Candida.* Infections.

Resumo

Introdução: As infecções relacionadas à assistência à saúde aumentam o risco de colonização por microrganismos multirresistentes (MDR). As infecções fúngicas são mais prevalentes em pacientes imunocomprometidos e portadores de doenças de base. A infecção por Covid-19 aumentou as internações em unidades de terapia intensiva (UTI), o que contribuiu para o aumento das coinfecções fúngicas e agravou a morbimortalidade dos pacientes. **Objetivos:** Este estudo teve como objetivo descrever a ocorrência de Candida spp. em pacientes com Covid-19 grave e medir a associação de fatores de risco para essas coinfecções. **Métodos**: Este artigo apresenta um estudo de coorte retrospectivo realizado em um hospital de referência no estado de Pernambuco. Foram avaliados os prontuários de 102 pacientes internados na UTI no período de junho a agosto de 2020, com diagnóstico de Covid-19 grave. A relação entre pacientes com infecções fúngicas e o grupo controle foi observada pela análise dos parâmetros laboratoriais. **Resultados:** Dos 102 pacientes avaliados, oito desenvolveram coinfecções por Candida spp.. Entre os oito casos, ocorreram três óbitos. Comparados com um grupo controle, os pacientes coinfectados com Candida spp. e a Covid-19 apresentou maior número de leucócitos totais, neutrofilia e maior uréia plasmática. **Conclusão:** Algumas alterações bioquímicas e hematológicas foram associadas à infecção por Candida spp.. Não detectamos resistência ao uso de antifúngicos como Fluconazol, Voriconazol, Caspofungina, Micafungina, Anfotericina B e Fluocitosina. A relação entre Acinetobacter baumannii com duas das três mortes de indivíduos diagnosticados com infecção fúngica sugere uma importante morbidade de infecções polimicrobianas em pacientes com Covid-19 grave.

Palavras-chave: Covid-19. SARS-CoV-2. Candida. Infecção Hospitalar.

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INTRODUCTION

Healthcare-associated infections (HAIs) are responsible for prolonging patients' hospital stay, increasing antimicrobial consumption, and consequently, colonisation and/or infection by multidrug-resistant microorganisms. Systemic fungal infections mainly affect immunocompromised patients and those with underlying diseases who require intensive care. Among the main risk factors for the occurrence of these infections is the performance of invasive procedures, such as surgery, mechanical ventilation, implantation of a central venous catheter, and haemodialysis, in addition to corticosteroid and prolonged antibiotic therapy. In recent years, there has been an increase in infections by *Candida auris*, a yeast that has gained prominence because of its antimicrobial resistance, and an increase in cases of non-albicans *Candida*.[1-3]

During the Covid-19 pandemic, triggered by SARS-CoV-2, healthcare professionals faced new challenges. Many patients with Covid-19 require hospitalisation, and in the most severe cases, many developed severe acute respiratory syndrome (SARS), requiring transfer to the Intensive Care Unit (ICU). They received corticosteroid therapy to reduce the inflammatory process and broad-spectrum antimicrobials to prevent bacterial co-infections, favouring the occurrence of fungal co-infections and increasing the risk of morbidity and mortality.[1,4-7].

Several studies have demonstrated the occurrence of invasive fungal co-infections in patients with severe Covid-19[4-6] and *Candida spp.* was the most frequently isolated fungus in 24.1% of 253 critically ill Covid-19 patients.[8] It has also been reported that patients hospitalized for Covid-19 are at risk for healthcare-associated infections (HAI), including candidemia.[9] In Brazil, Riche, Cassol and Pasqualotto[10] demonstrated an increase in frequency of candidemia in hospitalized patients with Covid-19 receiving corticosteroids with a high mortality rate. Aditionally, it has been showed that patients with Covid-19 who are immunosuppressed or have other pre-existing comorbidities are at a significantly higher risk of acquiring invasive fungal infections.[11]

It must be emphasised that few studies have demonstrated the main risk factors that justify the increase in the incidence of systemic infections by *Candida ssp.* in patients with Covid-19. Therefore, the objective of this study was to describe the occurrence of infections by *Candida spp.* in patients with severe Covid-19 and the associated risk factors for these co-infections.

METHODS

Population and place of study

This is a retrospective cohort study carried out at the Hospital das Clínicas of the Federal University of Pernambuco (HC-UFPE), located in the State of Pernambuco, Brazil. The medical records of 102 patients admitted to the ICU for Covid-19 (ICU-Covid) from June to August 2020 diagnosed with severe Covid-19 confirmed by RT-PCR for SARS- CoV-2 were analyzed. Patients were evaluated from admission to the ICU-Covid until discharge from this unit to the hospital ward or death. ICU admitted patients diagnosed with candidaemia or infection by *Candida spp.* in other biological materials (n = 08) had their clinical and laboratory data compared to the control group, characterized by patients also diagnosed with severe covid-19 and admitted to the same ICU, however, without infection by *Candida spp.* (n = 94). Thus, the study corresponded to a cohort of patients admitted to the ICU diagnosed with severe Covid-19. The results of the laboratory tests were collected daily or at the discretion of the ICU team, depending on the type of test and its applicability for the therapeutic management of the patient. Both individuals diagnosed with co-infection (fungal infection and SARS-CoV-2), and those who were not co-infected, had their exams collected following the same criteria of therapeutic care and diagnosis as the ICU team. Thus, the medians of each patient and the total number of patients were compared for each assay (between individuals with and without fungal infection). The following laboratory data were evaluated: antifungigram, haemoglobin concentration, total leukocytes, neutrophil count, lymphocyte count, platelets, D-dimer, lactate dehydrogenase (DHL), C-reactive protein (CRP), urea, and creatinine.

Laboratory diagnosis of infection by *Candida* spp.

Microbial growth of candidaemia was detected in blood culture samples using BACTEC FX (Becton Dickinson, New Jersey, USA), followed by microbial identification and resistance tests (antifungigram) using the VITEK 2 System (BioMérieux, Marcy-l' Étoile, France). The identification and antifungal activity of *Candida spp.* of other biological samples (tracheal secretion and urine) were performed directly using the VITEK 2 System. The antifungal agents tested were fluconazole, voriconazole, caspofungin, micafungin, amphotericin B, and flucytosine. Nosocomial infections associated with invasive devices by *Candida spp.* were defined as the laboratory detection of the microorganism after at least

48 hours of using devices such as mechanical ventilation, central catheters, or indwelling urinary catheters.[12]

Ethical Considerations

This research is in line with the ethical principles accepted by national (Resolution CNS 466/2012) and international (Declaration of Helsinki / World Medical Association) regulations. This study was approved by the Research Ethics Committee of the Hospital das Clínicas of (HC-UFPE) with an opinion number 4,579,183.

Statistical analyses

Clinical and laboratory data are presented using descriptive statistics, with continuous variables as means and interquartile ranges, and categorical variables as frequencies and percentages. We used the Mann-Whitney test to compare the differences between patients with *Candida spp.* and controls. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using the STATA software (StataCorp LLC, Texas, USA).

RESULTS

Eight patients (7.8%) diagnosed with severe Covid-19 in the ICU developed fungal infections caused by *Candida spp.*. The median age of these co-infected patients was 58.5 years (49.3–70.8). The incidence of *Candida spp.* in men and women was the same; however, deaths occurred in female patients. Most patients received antibiotic therapy (n = 8; 100%), corticosteroid therapy (n = 6, 85.7%), and antifungal therapy (n = 6; 85.7%). Regarding the analysed comorbidities, only diabetes (n = 2; 25%) and renal failure (n = 2; 25%) were included in the patient history, affecting different individuals. No individuals had infections caused by Human Immunodeficiency Virus, Hepatitis B, Hepatitis C, or malignant neoplasms. Regarding the three deaths, *Candida spp.* was diagnosed based on candidemia (n = 2; 25%) and tracheal secretions (n = 1; 12.5%). In addition, two of these individuals had co-infections with *Acinetobacter baumannii*. Additionally, most individuals with *Candida spp.* and Covid-19 had associated bacterial infections (n = 05; 62.5%). Clinical data and therapies used were not available for one patient (Table 1).

The main identified species of the genus *Candida* were *C. albicans* (n = 3; 37.5%), *C. tropicalis* (n = 3; 37.5%), and *C. parapsilosis* (n = 2; 25%). All species were sensitive to Fluconazole, Voriconazole, Caspofungin, Micafungin, Amphotericin B, and Fluocytosine. Additionally, haematological parameters, renal function, D-dimer, CRP, and LDH levels were compared among patients diagnosed with Covid-19, with and without *Candida spp.* (8 and 94 patients, respectively). Among the analytes evaluated, individuals with severe Covid-19 who developed *Candida spp.* infections had higher leukocyte and neutrophil counts and higher urea levels than those who did not develop the fungal infection (Table 2).

Table 1

Clinical and laboratory aspects addressed in individuals diagnosed with severe Covid-19 and co-infected with *Candida* spp.

Variables	Coinfected patients (N = 8)	%
Mean time to diagnose candidiasis (days) (mean ± SD)	14.4 ± 6.45	—
Genre (n = 8)		
Male	4	50
Female	4	50
Deaths (n = 8)	3	37.5
Deaths in females	3	37.5
Deaths in males	-	-
Comorbidities (n = 8)	4	50
Diabetes	2	25
Renal insufficiency	2	25
Drug treatment (n = 7)	7	100
Corticosteroid Therapy	6	85.7
Antibiotic Therapy	7	100
Antifungal Therapy	6	85.7
Candida infection isolation site (n = 8)		
Blood	4	50
Urine	2	25
Tracheal secretion	2	25
***Candida* spp.**		
Candida albicans	3	37.5
Candida parapsilosis	2	25
Candida tropicalis	3	37.5
Bacterial coinfection*		
Acinetobacter baumannii	02	25
Entreococcus faecalis	01	12.5
Pseudomonas aeruginosa	01	12.5
Klebsiella pneumonia	01	12.5
Enterobacter cloacae	01	12.5

*Some individuals had polymicrobial infections, while others did not have bacterial infections associated with *Candida* spp. co-infections and Covid-19.

Table 2

Comparison between laboratory parameters of patients admitted to the Intensive Care Unit (ICU) Covid-19 co-infected with *Candida* spp. vs. controls with Covid-19 without co-infection with *Candida* spp.

Variable*	*Candida* spp. coinfection (n = 8)	Controls (n = 94)	P- value**
Haemoglobin (g/dL)	11.30 (9.00; 14.13)	11.30 (9.03; 13.48)	0.995
Total leukocytes (cells/mm^3)	15945 (10485; 19928)	9970 (6060; 14170)	**0.015**
Neutrophils (cells/mm^3)	11785 (7475; 14400)	7120 (4000; 10860)	**0.036**
Lymphocytes (cells/mm^3)	1200 (686; 1450)	850 (600; 1500)	0.500
Platelets (mm^3)	258000 (171250; 328000)	231000 (151000; 323000)	0.763
D-dimer (ng/mL)	2150.0 (1762.5; 3415.0)	1798.4 (1420.0; 3850.0)	0.667
DHL (UI/L)	858.95 (500.90; 1522.48)	743.35 (524.13; 1103.63)	0.721
PCR (mg/dL)	9.00 (5.00; 28.60)	14.35 (6.03; 24.75)	0.710
Urea (mg/dL)	107.55 (82.48; 152.33)	47.45 (32.05; 93.73)	**0.010**
Creatinine (mg/dL)	2.9 (0.9; 5.5)	1.2 (0.7; 2.2)	0.095

*Results are presented as a median (Q1; Q3) **Mann-Whitney test for independent samples

DISCUSSION

Coinfection with *Candida spp.* and SARS-CoV-2 affected eight individuals (7.8%). Among those co-infected, there were three deaths (37.5%). A higher white blood cell count, neutrophilia, and higher plasma urea concentration were associated with infection by *Candida spp.* in patients with severe Covid-19 compared with a control group of patients diagnosed with severe Covid-19 without *Candida spp.* infection.

Opportunistic fungal infections are recurrent in ICUs, especially in immunocompromised systems, through superficial site infections, such as mucous membranes and invasive devices.[1,2] Several pathologies, such as Covid-19, can compromise the immune system, making it favourable for systemic fungal infections. In addition, extended hospital stays are associated with infections.[13-15] With the Covid-19 pandemic, an increased frequency of *Candida spp.* has become evident in intensive care units, especially in critically ill patients, owing to the immunocompromise caused by the viral infection.[1,5-14] The first case of invasive candidaemia and co-infection with Covid-19 was described at the beginning of the SARS-CoV-2 pandemic, in 2020 in Wuhan, China.[16] In Brazil, co-infections with *Candida spp.* and Covid-19 have gained notoriety due to the increase in cases of candidaemia in ICUs and the dissemination of the multidrug-resistant species *C. auris*, which has affected the prognosis of patients infected with SARS-CoV 2.[17]

In the present study, among the isolated species, the non-albicans Candida group represented five positive cultures (62.5%), with *C. tropicalis* and *C. parapsilosis*, while *C. albicans* represented three cases (37.5%). Other studies have revealed a higher frequency of *C. albicans* in co-infections with Covid-19.[18-20]. Despite the increasing frequency of *C. auris* in Brazil and co-infections with Covid-19,[13,21] infections by this species were not found in the group of patients analysed. Some Brazilian studies have shown a decreased sensitivity of *Candida spp*. to azole antifungals.[22, 23] However, the species found in this study were analysed using antifungigrams, which did not detect resistance to the use of antifungal agents such as Fluconazole, Voriconazole, Caspofungin, Micafungin, Amphotericin B, and Fluocytosine.

As previously mentioned, patients co-infected with *Candida spp.* and Covid-19 exhibited leukocytosis, neutrophilia, and higher urea levels than the control group (without fungal infection), confirming the findings of Kayaaslan et al. (2021).[24] This study showed neutrophilia and increased serum CRP and urea concentrations in patients with candidaemia and Covid-19 compared with the data from patients before the emergence of the SARS-CoV-2 pandemic. However, when evaluating all the patients in our research, with and without co-infection by *Candida spp.*, both groups showed a decrease in haemoglobin concentration, lymphopenia, and an increase in serum concentrations of D-dimer, CRP, and DHL.

These data are pertinent since Abolfotouh et al. (2022)[25] demonstrated higher mortality in hospitalised patients with Covid-19 associated with lymphopenia, neutrophilia, and elevated CRP. Although four patients had comorbidities, such as diabetes (n = 2) and renal failure (n = 2), Omrani et al. (2021)[26] did not show a correlation between these variables and *Candida spp.* co-infection. A significant increase in urea was reported in *Candida spp*. and Covid-19 co-infected patients, although there was no significant difference between creatinine values. Brookes & Power (2022)[27] discussed that increases in plasma urea concentration may be associated, among other factors, with cardiovascular system failure, hypovolaemia, and catabolism, in addition to reflecting a critical health condition.

This study identified that the co-infected patients had undergone drug treatment with corticosteroids, antibiotics, and antifungals, which corroborates the possibility of the risk of infection by *Candida spp.* Additionally, some studies have revealed that infections with other pathogenic agents increase the treatment period and mortality.[16] We observed that in two of the three identified deaths, there was an associated infection with *Acinetobacter baumannii*, a common bacterium in HAIs.

The number of *Candida spp.* infections has increased in hospitalised patients since the Covid-19 pandemic.[4,23] There is a relationship between invasive medical procedures, corticosteroid therapy, and immunocompromised patients as risk factors for fungal co-infections.[28] Thus, biomarkers related to a worse prognosis for patients admitted with severe Covid-19 are essential for the early identification of possible clinical worsening and the adoption of adequate medical care. The findings are based on a single- center retrospective cohort study with a relatively small sample size, which may not fully represent the broader population. Additionally, while the study identified risk factors for fungal co-infections, causation cannot be definitively established. Further research with larger and more diverse cohorts is needed to confirm these findings and explore additional factors contributing to fungal co-infections in Covid-19 patients.

CONCLUSIONS

Higher white blood cell count, neutrophilia, and higher plasma urea concentration were associated with infection by *Candida spp.* in patients with severe Covid-19. We did not detect resistance to the use of antifungal agents such as Fluconazole, Voriconazole, Caspofungin, Micafungin, Amphotericin B, and Fluocytosine. Two of the three identified deaths, there was an associated infection with *Acinetobacter baumannii*, a common bacterium in Healthcare-associated infections (HAI).

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