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*Coronavirus Pandemic*

# Epidemiology of invasive candidiasis before and during the COVID-19 pandemic at a hospital in southeastern Brazil

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## Abstract

Introduction: Invasive candidiasis is an important cause of nosocomial infection and recent studies have shown an increase in the number of cases during the coronavirus disease 2019 (COVID-19) pandemic. The present study aimed to evaluate the epidemiology and incidence of invasive candidiasis before and during the COVID-19 pandemic at a reference tertiary hospital in Brazil.

Methodology: A retrospective observational study was performed with 148 patients infected with *Candida* spp.

Results: The incidence of invasive candidiasis was 3.43 cases per 1000 admissions in the pre-pandemic period and 4.54 cases per 1000 admissions in the pandemic period, with a particularly high incidence in the intensive care unit. Compared to the pre-pandemic period, patients presented more frequently with immunosuppression ($p = 0.01$), sepsis ($p = 0.03$), and need for mechanical ventilation ($p = 0.01$) during the pandemic. The prevailing type of *Candida* spp. infection was candidemia, mostly by *C. albicans*. Invasive candidiasis was associated with high mortality; 52% of the infected patients died from this disease in the pre-pandemic period, while 62% died in the pandemic period. COVID-19, mechanical ventilation, and sepsis were significantly associated with mortality ($p = 0.008$, $p < 0.001$, and $p < 0.001$ respectively).

Conclusions: A high incidence of *Candida* infection was observed at a tertiary general hospital in Brazil between 2018 and 2022. An increase in incidence of *Candida* infection during the COVID-19 pandemic was associated with a greater number of critical patients. Sepsis, mechanical ventilation, and COVID-19 were related to higher mortality in patients with invasive candidiasis.

**Key words:** invasive candidiasis; candidemia; COVID-19.

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## Introduction

Invasive candidiasis is an opportunistic infection by microorganisms of the *Candida* spp. in the bloodstream (candidemia); and/or in sterile sites such as peritoneum, pleura and intra-abdominal organs and tissues (deep candidiasis). The spectrum of deep candidiasis includes abdominal abscess, peritonitis, osteomyelitis, pyelonephritis, endocarditis, and meningoencephalitis; infections in other sites such as the oropharynx and vulvovaginal candidiasis are not considered invasive [1,2]. The five most frequent pathogenic species of *Candida* are *C. Albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* [3].

Invasive candidiasis' impact on public health is evident from its frequency in hospitalized patients, given that it has been identified as the fourth leading cause of bloodstream infection. Candidemia also has a major impact on morbidity and mortality, increasing the mortality of hospitalized patients by approximately 50%, as well as the length of hospital stay [4].

Several risk factors for candidemia are well-established; and include total parenteral nutrition, acute kidney injury, septic shock, central venous catheter, and exposure to broad-spectrum antimicrobials [5]. Recent studies have shown that during the coronavirus disease 2019 (COVID-19) pandemic an increase in the rate of healthcare-associated infections, including invasive candidiasis [6–8], was identified.

The aim of this study was to compare the incidence of invasive candidiasis before and during the COVID-19 pandemic at the Unicamp Clinical Hospital, as well as to evaluate the epidemiology, clinical characteristics, and outcomes in both periods.

## Methodology

A retrospective observational study was carried out with data from September 2018 to June 2022. This research constitutes a sub-project of the multicenter study: project for the establishment of a collaborative reference and research system for the diagnosis of resistant fungal infections in Brazil. The study site was the Clinical Hospital of the State University of Campinas (Unicamp), a tertiary general hospital of reference for the metropolitan region of Campinas,

which comprises a population of approximately 6 million people. The hospital had an average of 477 beds, and, during the pandemic period, surgeries and elective procedures were limited in order to provide better care for an increasing number of patients diagnosed with COVID-19.

The MIRE project, through hospital infection control teams, gathered information about cases of invasive fungal infections in four centers located in the city of Campinas (Unicamp Clinical Hospital, Ouro Verde Hospital Center, Boldrini Children's Center, and Mario Gatti Municipal Hospital). This information was then is stored in a specific database called the Research Electronic Data Capture (REDCap) platform. Patients diagnosed with invasive candidiasis during the period of interest were selected for the present study. The criteria for inclusion of patients were to have: i) diagnosis of candidemia and/or deep candidiasis; ii) age of ≥ 18 years; and iii) been admitted to Unicamp Clinical Hospital. This hospital was chosen since it encompassed the majority of cases of invasive candidiasis among all hospitals that are part of the MIRE project as the main hospital in the region and provided access to extensive data for research. Incomplete data were excluded from the study.

COVID-19 was diagnosed through polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); and *Candida spp*. infection was diagnosed through cultures, performed by automated microbiological systems BacT/ALERT 3D FA and PF bottles (bioMérieux, Inc., Durham, NC, USA). For identification, the isolates were cultured on Sabouraud dextrose agar (SDA; Difco, Sparks, Maryland, USA) at 35 °C for 48 hours before the tests. Isolates recovered from cultures were identified according to their macromorphology on Sabouraud dextrose agar (Difco, Sparks, Maryland, USA); and microscopic morphology on cornmeal Tween 80 agar, germ tube test, and VITEK™ 2 (bioMérieux, Craponne, France). Candidemia was determined by identifying one or more species of the genus *Candida* in at least one blood culture; while deep candidiasis in the present study comprised of the identification of one or more species of *Candida spp*. in cultures of peritoneal fluid, pleural fluid, abscesses, bone biopsies, or vitreous humor. Patients were included in the study only once, regardless of the number of positive cultures.

The data on cases of interest was structured. The study compared two periods: between September 2018 and February 2020, defined as the pre-pandemic period; and between March 2020 and June 2022, the COVID-19 pandemic period. The patients were divided into three groups according to the sectors where they were hospitalized at the time of diagnosis of fungal infection – adult intensive care unit (ICU), clinical ward, or surgical ward. To calculate the incidence of invasive candidiasis, the total number of hospitalized patients and patient-days at each of these sectors in the pre-pandemic and pandemic periods was obtained from the public database of the Unicamp Clinical Hospital. Clinical outcome was evaluated by the mortality rate, defined as death prior to discharge from the hospital stay in which the patient was infected with *Candida spp*.

Demographic, clinical and microbiological data of patients with invasive candidiasis were compared and statistical analysis was performed using the Epi-info software version 3.01. Categorical variables were evaluated using the mild-*p* test and continuous variables using Student's t-test, for which a $p$ value < 0.05 was considered statistically significant.

This study was presented to the Research Ethics Committee and was approved (CAAE 64179422.9.0000.5404) as a sub-analysis of the 'Project for the establishment of a collaborative reference and research system for the diagnosis of resistant fungal infections in Brazil' (CAAE 92692418.9.0000.5404). This project was approved by the Medical Ethics Committee, and all participants agreed to their inclusion through a free and informed consent term.

## Results

The REDCap database included 208 patients diagnosed with candidemia or deep candidiasis between

**Table 1.** Incidence of invasive candidiasis and candidemia at Unicamp Clinical Hospital according to hospitalization sector from 2018 to 2022.

| *Candida* infection | Pre-pandemic | | | | COVID-19 Pandemic | | | |
|---|---|---|---|---|---|---|---|---|
| | ICUa | Clinical ward | Surgical ward | Total | ICU[a] | Clinical ward | Surgical ward | Total |
| **Episode per 1000 patients** | | | | | | | | |
| Invasive candidiasis | 19.53 | 2.38 | 1.74 | 3.43 | 21.43 | 2.08 | 1.65 | 4.54 |
| Candidemia | 14.64 | 2.10 | 0.87 | 2.48 | 16.07 | 1.39 | 0.63 | 3.08 |
| **Episode per 1000 patients** | | | | | | | | |
| Invasive candidiasis | 1.15 | 0.21 | 0.29 | 0.38 | 1.18 | 0.19 | 0.18 | 0.41 |
| Candidemia | 0.86 | 0.18 | 0.15 | 0.27 | 0.88 | 0.13 | 0.07 | 0.28 |

ICU, intensive care unit; COVID-19: coronavirus disease 2019. [a]Adult intensive care unit.

**Table 2.** Distribution of invasive candidiasis cases according to clinical and epidemiological characteristics in the COVID-19 pre-pandemic and pandemic periods.

| Characteristics | Pandemic period | | | | Pre-pandemic period | |
|---|---|---|---|---|---|---|
| | Total n (%) (n=87) | Without COVID-19 n (%) (n = 70) | With COVID-19 n (%) (n= 17) | $P^a$ | Total n (%) (n = 61) | $P^{a,b}$ |
| Age, mean | 58.9 | 59.9 | 54.7 | 0.2165 | 56.21 | 0.3108 |
| Gender, male | 56 (64.37) | 46 (65.71) | 10 (58.82) | 0.6019 | 36 (59.02) | 0.5143 |
| **Comorbidity** | | | | | | |
| Diabetes | 30 (34.48) | 22 (31.43) | 8 (47.06) | 0.2438 | 21 (34.43) | 0.9969 |
| Hypertension | 45 (51.72) | 34 (48.57) | 11 (64.71) | 0.2486 | 25 (40.98) | 0.2036 |
| Coronary artery disease | 11 (12.64) | 8 (11.43) | 3 (17.65) | 0.5030 | 4 (6.56) | 0.2422 |
| Heart failure | 8 (9.19) | 6 (8.57) | 2 (11.76) | 0.6742 | 7 (11.47) | 0.6571 |
| Chronic pulmonary disease | 6 (6.90) | 6 (8.57) | 0 | 0.2596 | 5 (8.20) | 0.7687 |
| Chronic renal disease | 16 (18.39) | 11 (15.71) | 5 (29.41) | 0.2217 | 12 (19.67) | 0.8428 |
| Malignity | 14 (16.09) | 13 (18.57) | 1 (5.88) | 0.2206 | 17 (27.87) | 0.0909 |
| Imunossuppression | 30 (34.48) | 24 (34.29) | 6 (35.29) | 0.9271 | 10 (16.39) | 0.0148 |
| Mechanical ventilation | 50 (57.47) | 35 (50.00) | 15 (88.24) | 0.0038 | 22 (36.07) | 0.0111 |
| Sepsis | 53 (60.92) | 40 (57.14) | 13 (76.47) | 0.1534 | 26 (42.62) | 0.0301 |
| Corticosteroid use | 23 (26.44) | 13 (18.57) | 10 (58.82) | 0.0019 | 11 (18.03) | 0.2395 |
| Central venous catheter | 78 (89.65) | 60 (85.71) | 17 (100) | 0.0992 | 56 (91.80) | 0.6815 |
| Parenteral nutrition | 20 (22.99) | 17 (24.29) | 3 (17.65) | 0.5956 | 13 (21.31) | 0.8179 |
| Gastrointestinal surgery | 29 (33.33) | 28 (40.00) | 1 (5.88) | 0.0055 | 25 (40.98) | 0.3484 |
| *Candida* colonisation | 26 (29.88) | 17 (24.29) | 9 (52.94) | 0.0299 | 10 (16.39) | 0.0616 |

[a]Mild *p* if categorical variable; Student's t test if continuous variable; [b]Comparison between pre-pandemic period and total pandemic period; COVID-19: coronavirus disease 2019.

September 2018 and June 2022. Of those patients, 60 were excluded because they were not hospitalized at the Unicamp Clinical Hospital, were < 18 years of age, or had incomplete data. Hence, the present study evaluated 148 patients with invasive candidiasis at the Unicamp Clinical Hospital. The total incidence of invasive candidiasis (Table 1) was 3.43 cases per 1000 admissions in the pre-pandemic period, and 4.54 cases per 1000 admissions in the pandemic period. When comparing hospitalization units, there was a higher incidence of invasive candidiasis in the ICUs, with 21.43 cases per 1000 admissions in the pandemic period. The incidence of *Candida* infections during the pandemic decreased in the clinical and surgical ward and increased in the ICU.

Demographic data, clinical characteristics and risk factors associated with cases of invasive candidiasis in the pre-pandemic and pandemic period are summarized in Table 2. The mean ages of patients with invasive candidiasis in the pre-pandemic and pandemic period were 56 and 58 years, respectively; and the most prevalent comorbidities in both periods were hypertension and diabetes. There was a higher rate of patients with immunosuppression ($p = 0.01$) and sepsis ($p = 0.03$), as well as a greater need for mechanical ventilation ($p = 0.01$), during the pandemic period. When comparing patients with and without a diagnosis of COVID-19 during the pandemic, patients with COVID-19 were more often under mechanical ventilation ($p = 0.003$), required the use of corticosteroids more frequently ($p = 0.0019$), and had fewer abdominal surgeries ($p = 0.005$).

The distribution between the forms of invasive candidiasis (candidemia or deep candidiasis) and causative species of *Candida* spp. are presented in Table 3. The most frequent type of *Candida* infection both before and during the pandemic was candidemia, concerning approximately 70% of infections. When

**Table 3.** Distribution of forms of infection by *Candida* spp. in the COVID-19 pre-pandemic and pandemic periods, and clinical outcome.

| Forms of infection | Pandemic period | | | | Pre-pandemic period | |
|---|---|---|---|---|---|---|
| | Total (n = 87) | Without COVID-19 n (%) (n = 70) | With COVID-19 n (%) (n = 17) | *p* | Total (n = 61) | $p^a$ |
| **Candidemia** | 59 (67.82) | 44 (62.86) | 15 (88.23) | 0.0440 | 44 (72.13) | 0.5828 |
| **Deep candidiasis** | 28 (32.18) | 26 (31.14) | 2 (11.76) | | 17 (27.87) | |
| **Candida species** | | | | | | |
| *Candida albicans* | 39 (44.83) | 31 (44.29) | 8 (47.06) | 0.8389 | 31 (50.82) | 0.4785 |
| *Candida tropicalis* | 22 (25.28) | 20 (28.57) | 2 (11.76) | 0.1620 | 12 (19.67) | 0.4348 |
| *Candida glabrata* | 11 (12.64) | 8 (11.43) | 3 (17.65) | 0.5030 | 11 (18.03) | 0.3764 |
| *Candida parapsilosis* | 11 (12.64) | 8 (11.43) | 3 (17.65) | 0.5030 | 7 (11.47) | 0.8443 |
| *Candida krusei* | 6 (6.90) | 5 (7.14) | 1 (5.88) | 0.9267 | 3 (4.92) | 0.6513 |
| **Others**[b] | 9 (10.84) | 7 (10.00) | 2 (11.76) | 0.8028 | 4 (6.56) | 0.4469 |
| **Death** | 54 (62.07) | 39 (55.71) | 15 (88.23) | 0.0122 | 32 (52.45) | 0.2503 |

[a]Comparison between pre-pandemic period and total pandemic period. [b]*C. kefyr, C. orthopsilosis, C. lusitaniae, C. africana, C. dubliniensis, C. guilliermondii, C. Fabianii.* COVID-19: coronavirus disease 2019.

comparing patients with and without COVID-19, those with COVID-19 had a significantly higher rate of candidemia (88% of cases) compared to patients without COVID-19 (62% of cases; $p = 0.04$), in which deep candidiasis represents almost one third of the cases. The most prevalent *Candida*. species was *C. albicans*, identified in almost half of the cultures, followed by *C. tropicalis*. Invasive candidiasis at Unicamp Clinical Hospital was related to high mortality; as 52% of infected patients died from this disease in the pre-pandemic period, and 62% in the pandemic period.

Table 4 shows the distribution of clinical and epidemiological factors in patients with invasive candidiasis who survived or died. The presence of COVID-19, mechanical ventilation, and sepsis were significantly associated with mortality ($p = 0.008$, $p < 0.001$, and $p < 0.001$ respectively), while invasive candidiasis that occurred in patients with abdominal surgery was associated with a lower death rate ($p = 0.005$).

## Discussion

Invasive candidiasis has acquired a prominent position among the causes of healthcare-associated infection (HAI). Brazil is a country with high incidence of candidemia, which varies according to the region of the country, the type of hospital management, and the effectiveness of HAI prevention and control measures [9]. Recent studies in Brazil show that incidence rates ranged from 1.2 to 2.23 episodes per 1000 admissions [10–12]. Although the present study demonstrates a high incidence of candidemia (2.48 patients per 1000 admissions pre-pandemic and 3.08 patients per 1000 admissions during the pandemic), there was a decrease when compared to the incidence found in a study from 2006 to 2010 at Unicamp Clinical Hospital, when candidemia occurred in 3.6–6.0 patients per 1000 admissions [13].

The COVID-19 pandemic has triggered changes in the epidemiology of global invasive candidiasis. Several studies confirm the finding of increased rates of candidemia during the pandemic, even in patients without COVID-19 [8,14,15]. The work by Nucci *et al.* indicated that the incidence of candidemia went from 1.54 per 1000 admissions in the pre-pandemic period (January 2019 to February 2020) to 7.44 per 1000 admissions in the pandemic period (March to September 2020) [15]. When comparing the incidence of candidemia in patients with and without a diagnosis of COVID-19, a higher rate was observed in patients with COVID-19 [15–17]. Few studies differentiate the incidence of *Candida* spp. infection depending on the hospitalization sector, as described in our work. As expected, the occurrence of invasive candidiasis was higher in ICUs (approximately 2% of patients admitted to this department), but the incidence in wards was not negligible. The growth in the total incidence during the pandemic, as shown in the present study, was likely related to the increase in the number of ICU patients and

**Table 4.** Clinical outcome (death or survival) of cases of invasive candidiasis diagnosed at Unicamp Clinical Hospital according to clinical-epidemiological characteristics.

| | **Death, n (%) (n = 86)** | **Survival, n (%) (n = 62)** | ***p*** |
|---|---|---|---|
| Age, mean | 59.39 | 55.52 | 0.1366 |
| Gender, male | 53 (61.63) | 39 (62.90) | 0.8782 |
| Comorbidity | | | |
| Diabetes | 33 (38.37) | 18 (29.03) | 0.2448 |
| Hypertension | 44 (51.16) | 26 (41.93) | 0.2738 |
| Coronary artery disease | 12 (13.95) | 3 (4.84) | 0.0736 |
| Heart failure | 9 (10.46) | 6 (9.68) | 0.8890 |
| Chronic pulmonar disease | 7 (8.14) | 4 (6.45) | 0.7231 |
| Chronic renal disease | 15 (17.44) | 13 (20.97) | 0.5943 |
| Malignity | 14 (16.28) | 17 (27.42) | 0.1086 |
| Immunosuppression | 24 (27.91) | 16 (25.81) | 0.7837 |
| Mechanical ventilation | 56 (65.12) | 16 (25.81) | < 0.0001 |
| Sepsis | 60 (69.77) | 19 (30.64) | < 0.0001 |
| Corticosteroid use | 24 (27.91) | 10 (16.13) | 0.0964 |
| Central venous cateter | 81 (94.19) | 53 (85.48) | 0.0873 |
| Parenteral nutrition | 20 (23.26) | 13 (20.97) | 0.7506 |
| Gastrointestinal surgery | 22 (25.58) | 32 (51.61) | 0.0014 |
| Candida colonisation | 26 (30.23) | 10 (16.13) | 0.0500 |
| *Candida albicans* | 40 (46.51) | 30 (48.39) | 0.8238 |
| *Non-albicans Candida* | 50 (58.14) | 36 (58.06) | 0.9917 |
| COVID-19 | 15 (17.44) | 2 (3.23) | 0.0064 |

COVID-19: coronavirus disease 2019.

to differences in their clinical features, since the incidence reduced in clinical and surgical wards. The ICU study by Kayaaslan *et al.* demonstrated an incidence of candidemia of 1.9% in patients with COVID-19 and 0.5% in patients without COVID-19 [7].

A meta-analysis on invasive candidiasis, with 34 studies prior to the COVID-19 pandemic, identified that the main risk factors associated with infection in critically ill patients were the use of broad-spectrum antimicrobials, blood transfusion, colonization by *Candida* spp., central venous access, and total parental nutrition [18]. Such association with blood transfusion may be connected to a secondary immune dysfunction [19]. Other causes of immunosuppression, such as malignancy [20], chronic kidney disease [21], and diabetes [22], also increase the risk of invasive candidiasis. Colonization by *Candida* spp. and central venous access enable this microorganism, that has the ability to form biofilm, to cause infection. *Candida* spp. can also proliferate in parenteral nutrition preparations [23].

Studies have shown an increase in some risk factors for candidemia in patients with COVID-19, such as central venous access, total parenteral nutrition, use of corticosteroids, and septic shock; while patients without COVID-19 and with candidemia have more hepatic diseases and infections or abdominal surgeries [8,24]. The present study found a higher rate of corticosteroid use and colonization by *Candida* spp. and a lower rate of abdominal surgeries in patients with COVID-19 and invasive candidiasis. Taking into account that abdominal interventions have been linked to the development of intra-abdominal candidiasis [25], the fact that a greater rate of abdominal surgeries were performed in patients without COVID-19 could explain why there was higher frequency of deep candidiasis in these patients.

During the COVID-19 pandemic period at Unicamp Clinical Hospital, an increase in the frequency of mechanical ventilation, sepsis and immunosuppression was observed in patients with invasive candidiasis. This increase in the severity of hospitalized patients and risks factors for *Candida* spp. infections related to COVID-19, in addition to the burden of the pandemic on health services, are the most likely reasons for the higher incidence of invasive candidiasis during the pandemic.

The present study also evaluated the distribution of species of *Candida* spp. in the pre-pandemic and pandemic periods. A higher frequency of *Candida albicans* was observed and found in almost half of the cultures, similar the pattern previously observed at Unicamp Clinical Hospital [13]. Other studies in Spain [8] and Turkey [7,26] demonstrated a similar distribution, while there was a higher incidence of non-albicans *Candida* in some studies in the United States [16,24], Italy [17], and Greece [14]. A review article on fungal infections in Latin America showed that the frequency of *Candida* spp. found in blood cultures is similar to that observed in the present study, as *C. albicans* was the most frequent, followed by *C. tropicalis* and *C. parapsilosis* [27].

Candidemia has been related to high mortality, with rates that can exceed 90% depending on the hospitalization sector studied, early treatment, and patient comorbidities. The study by Kayaaslan *et al.* reported the occurrence of deaths in 92.5% of patients admitted to the ICU with COVID-19, which was significantly higher than the proportion of deaths in patients without COVID-19 (79.4%) [7]. Similar to the present study, several other studies showed a trend of higher mortality when patients with candidemia were also co-infected with SARS-CoV-2, with rates of 75% [16], 73.9% [8], and 62.5% [24]. A 2012 review noted a comparatively low mortality due to invasive candidiasis (31.4%), and identified the following risk factors for death – advanced age, rising acute physiology and chronic health evaluation II (APACHE II), immunosuppressive treatment, malignancy, neutropenia, total parenteral nutrition, mechanical ventilation, and renal or hepatic dysfunction [28].

The present study had some limitations, including the fact that it was a single-center retrospective study. We were not able calculate the incidence of invasive candidiasis separately in patients with COVID-19, as there was no data available on the total number of hospitalized patients with COVID-19 in the period under evaluation. Finally, the study could only evaluate general mortality given that the data did not provide information on the time of a patient's death after the cultures tested positive for *Candida* spp.

## Conclusions

A high incidence of *Candida* infection was observed at a Brazilian tertiary general hospital between 2018 and 2022, mainly in ICUs. During the COVID-19 pandemic, this incidence increased, with a greater number of patients who had sepsis, used mechanical ventilation, and were colonized by *Candida* spp. compared to the pre-pandemic period; and these factors were related to the higher mortality in patients with invasive candidiasis. SARS-CoV-2 infection was associated with higher mortality. Knowledge about the epidemiology, clinical and microbiological

characteristics, and about the many factors associated with mortality from *Candida* spp. is crucial for the care of hospitalized patients, in order to prevent infection and provide early treatment.

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