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COVID-19 and candidemia: high mortality in critically Ill patients

Abstract

The purpose of this study was to describe the clinical characteristics and outcomes of patients with SARS-CoV-2 infection with concomitant candidemia. A retrospective study was conducted where clinical characteristics, risk factors, and mortality were described. Absolute and relative frequencies were used for qualitative data, whereas means and medians with standard deviations were calculated for the quantitative variables. Prevalence, risk factors, and mortality were determined. A total of 21 patients were included, all of which patients had central venous catheters and had received antibiotics; 76% (16/21) used steroids. 33% had a Candida non-albicans infection. The median days until the first isolation were 21.32 days. Mortality was 67%. The most important risk factors for this disease and its mortality are ICU admissions, prolonged hospital stays, invasive mechanical ventilation, use of antibiotics and steroids, and comorbidities such as Diabetes mellitus. In our study, we found that there is a significant mortality rate in COVID-19 and candidemia-infected patients. Concomitant infections and factors that may aggravate COVID-19 should be considered in the critical care setting, to detect and treat them promptly.

Keywords: Candidemia, COVID-19, mortality, candida non-albicans, candida albicans

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Introduction

At the end of 2019, we had to face a big challenge in the world of humanity, a pandemic caused by the SARS-CoV-2 virus. In the beginning, the initial identification[1] and subsequent implementation of diagnostic methods[2] were extremely fast, but the pandemic could not be contained, even though.[3] This is because SARS-CoV-2 has a more efficient spread than the previous one, but also because asymptomatically infected individuals and pre-symptomatic patients are contagious too.[4]

The coronavirus disease 2019 (COVID-19) clinical course can be a mild upper respiratory illness or inclusive of a fulminant respiratory failure requiring mechanical respiratory support. Also, this disease can have complications in the kidney, hematological systems, and central nervous system (CNS), which carry the risk of developing superinfections. Some patients have the highest risk for severe disease, such as those with such as obesity, hypertension, and diabetes mellitus (DM).[5,6] Approximately 5 to 32% of patients with COVID-19 require an ICU, a percentage that changes between published studies.[7,8]

COVID-19 has been recognized as an important cause of acute respiratory distress syndrome (ARDS), with a substantial predisposition to bacterial and fungal superinfections. Recent research has shown an increase in the incidence of candidemia, especially in critically ill COVID-19 patients.[3] A meta-analysis found that the four most frequent fungal agents involved in COVID-19-infected individuals were Candida albicans, Candida glabrata, Aspergillus flavus, and Aspergillus fumigatus.[9]

Invasive candidiasis is the most prevalent yeast infection worldwide, particularly when referring to hospitalized and critical patients. This infection has a mortality of up to 40%, despite the new and improved antifungal treatments that have been developed over recent years.[10]

Candidemia is one of the fourth most frequent blood infections in the ICU setting. It is known that this fungal infection is the ten most important causes of infectious blood diseases, with a higher incidence in pediatric and geriatric individuals.[10,11] In the United States, Candida species are responsible for 8-10% of all bloodstream infections, and this candidemia is known to occur in the ICU in 30–35% approximately.[12,13] There are at least 15 Candida species that contribute to the burden of human disease, however, most infections caused by this genus occur due to Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei species. In the last few years, Candida auris has been identified as a relevant pathogen, causing many nosocomial outbreaks.[11]

Even though Candida albicans remains the main causative agent, it is suggested that non-albicans species could represent around 50% of all cases of candidemia cases.[11]

It does not know defects in immune cells that could be necessary for immunity in candida infections. This suggests that risk factors known before for this invasive fungal infection might be the same factors that make COVID-19 patients more susceptible to developing this fungal infection including prolonged ICU stays, central venous catheters, and the use of broad-spectrum antibiotics.[14]

The purpose of this study is to describe the clinical characteristics and outcomes of SARS-CoV-2 infected patients with concomitant candidemia, performed and analyzed at the National Institute of Respiratory Diseases (INER) in Mexico City, Mexico.

Materials and methods

A retrospective observational study was conducted, including all patients between 18 and 99 years of age who had a diagnosis of COVID-19, confirmed by RT-PCR SARS-CoV-2, positive blood culture with Candida s.p.p., and received medical care in the period between February and December 2020, during which time 1,917 patients with moderate and severe COVID-19 were treated. Patients who did not receive treatment at INER and those who did not have a complete medical history were excluded.Clinical and demographic data collection was performed through clinical review of clinical records of patients with a positive blood culture for candida. The clinical (fever, septic shock) and sociodemographic (age, gender,

occupation) data was obtained and recorded in an Excel database and statistical analysis was performed using IBM SPSS 27.

Results are presented through descriptive statistics; medians with ranges and/or averages with standard deviations were used for quantitative variables and qualitative data, frequencies and percentages were used. As for bivariate analysis, patients were divided into two groups: patients with yeasts identified as Candida albicans. and patients with infection by non-albicans candida species; qualitative results were compared through an X2 test or Fisher's Exact Test. As for the qualitative variable analysis, T of Student and/or Mann-White U tests were performed. A p-value <0.05 was considered statistically significant. Data is presented along p-value and odds ratio with a confidence interval of 95%.

Ethical aspects

This study follows the ethical guidelines established for the use of patient information and has been approved by the INER ethical committee.

Results

A total of 21 patients with a COVID-19 diagnosis had objective candidemia. Average age was 58.19 years (± 12.02). A higher number of cases was observed in male patients with a male/female ratio of 2.5:1. Table 1 describes the baseline clinical characteristics, microbiological characteristics, and treatment modalities of patients with candidemia.

Table 1 Sociodemographic data in patients

Sociodemographic data in patients						
	Total	**Candida albicans (N=14)**	**Candida species (N = 7)**	**P**	**OR**	**IC 95%**
	(N=21)					
Men	71% (15/21)	71% (10/14)	71% (5/7)	P=0.7	1	0.13-7.45
Median Age	58.19 (± 12.02)	55.57 (± 4.54)	63.43 (± 4.89)	P= 0.33		
COMORBIDITIES	67% (14/21)	64% (9/14)	71% (5/7)	P= 0.57	0.06	0.73-60.52
Diabetes Mellitus	42% (9/21)	36% (5/14)	57% (4/7)	P= 0.31	0.41	0.06-2.66
Hypertension	28% (6/21)	29% (4/14)	29% (2/7)	P= 0.68	1	0.13-7.45
CLINICAL FINDING						
	Total (N=21)	Candida albicans (N=14)	Candida species (N = 7)	P	OR	IC 95%
fever	95% (20/21)	93% (13/14)	100% (7/7)	P = 0.66	0.65	0.47-0.89
LEUKOCYTES (103/mm3)	18,20 (± 14,51)	19,7 (± 23,01)	15,4 (± 5,2)	P=0.11		
NEUTROPHILES (103/mm3)	10,7 (± 4,6)	9,40 (± 3,81)	12,98 (± 5,23)	P= 0.12		
LYMPHOCYTES (103/mm3)	1,24(± 1.23)	1.27 (± 1.50)	1.17 (± .98)	P= 0.77		
CREATININE (MG/DL)	0.66 (±1.09)	0.71 (± 0.32)	1.39 (± 0.18)	P= 0.02		
Risk factors for candidal bloodstream infections						
	Total (N=21)	Candida albicans (N=14)	Candida species (N = 7)	P	OR	IC 95%
ANTIBIOTICS	85.7% (18/21)	85.7% (12/14)	85.7% (6/7)	0.73	1	0.07-13.36
Ceftriaxone	81% (17/21)					
Meropenem	62% (13/21)					
Clarithromycin	52% (12/21)					
Trimethoprim/Sulfamethoxazole	32% (8/21)					
Colistin	24%(5/21)					
Vancomycin	24%(5/21)					
Azithromycin	19%(4/21)					
Piperacillin/Tazobactam	19% (4/21)					
Linezolid	19% (4/21)					
Cefepime	10 %(2/21)					
Ceftazidime	10% (2/21)					
Ertapenem	5% (1/21)					
STEROIDS	76.2% (16/21)	71.4% (10/14)	85.7% (6/7)	P= 0.46	0.44	0.13-0.72
MECHANICAL VENTILATIONS	100% (21/21)					
CENTRAL VENOUS CATHETER	100% (21/21)					
ICU STAY	24% (5/21)	29% (4/21)	14.3% (1/7)	P= 0.44	2.4	0.25-26.82
OUTCOMES						
	Total (N=21)	Candida albicans (N=14)	Candida species (N = 7)	P	OR	IC 95%
TREATMENT	67% (14/21)	71% (10/14)	57% (4/7)	0.48	1.87	0.28-12.44
DURATION OF TREATMENT (DAYS)	9.49 (± 7,09)	9,5 (± 8.23)	9.24 (± 3.8)	0.03		
ANTIFUNGALS	61.9% (13/21)					

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Table 1 Continued...

OUTCOMES						
- Caspofungin	4.8% (1/21)	71.4% (10/14)	42.9 (3/7)			
- Fluconazole			14.3% (1/7)			
CANDIDA ISLATION TIME SINCE ADMISSION	17.98 (± 14.51)	25 (± 16.17)	14.41 (± 7.22)	0.08		
HOSPITAL STAY	23.88 (± 22.83)	35.99 (± 16.17)	19.64 (± 7.22)	0.01		
MORTALITY	67% (14/21)	64%(9/14)	71.% (5/7)	0.57	0.72	0.10-5.16

All patients had central venous access catheters and antibiotics were used in 18 subjects. A high percentage of subjects were taken on corticosteroid therapy, The average number of days on steroids was 6.75 (± 3.33), methylprednisolone was used in 11, and 6 patients were treated with hydrocortisone. Of those 21 cases, 67% (14/21) had a history of cardiometabolic comorbidities, type 2 diabetes mellitus being the most common.

Isolated species from blood cultures were Candida albicans (n=14), Candida tropicalis (n=2), Candida lipolytica (n=2), Candida glabrata (n=1) Candida spherica (n=1), and Candida parapsilosis (n=1). The median time to first isolate yeast was 21.32 days ± 14.51 and the average length of stay in hospital was 30,54 days ± 22.83. Of these 21 yeasts, 48% (10/21) of the yeasts were identified as candida by multiplex PCR (BCID FilmArray® sepsis panel), two hours after their detection in blood cultures. The mean time between the isolation of fungi and the traditional determination of the species using a VITEC 2® system was 2.9 ± 2.4 days.

Fever and leukocytosis were the most common clinical findings in patients with candidemia. 67% (14/21) of the patients in our study were managed with antifungal agents. 13 were treated with caspofungin, with a median length of treatment of 9,49 days ± 7.09. Overall mortality was 67%.

The comparison of clinical characteristics and outcomes between patients with candidemia with Candida albicans and other Candida species is also found in Table 1. Creatinine levels were higher in patients with a yeast infection identified as non-albicans. Patients with candida albicans stayed longer in the hospital, a median of 35.99 days, compared to 19 days in infections by non-albicans species. The latter also had higher survival rates; however, the difference was not significant.

Discussion

In the global pandemic of COVID-19, we have seen a relatively high number of patients with ARDS. In the first months of 2020, the Mexican Health Ministry designated the transformation of health institutions, mainly in Mexico City because saturation of health centers to exclusively treat COVID-19 patients. The hospital transformation increased the capacity to attend to patients in critical condition, with 250 beds and 200 ventilators.[15]

In INER, from February to December 2020, 1917, critically ill patients were treated. During this time, 21 candidemias were documented, a prevalence of 1%. The prevalence of candidemia varies by country and region, European countries such as Spain reported a rate of 0.7% (7/989)[16] China being the country with the highest frequency of cases, 23.5%.[17] Some authors reported an increased rate of candidemia in patients with SARS-CoV-2 compared with historical non–COVID–19 studies. Rates of candidemia were significantly higher in patients with COVID-19 (10.97 [6.79–16.76] vs 1.48 [1.10–1.95] cases per 10.000 PDFU; P < .001).[18]

The Candida genus is characterized by commensal fungi, which make up some skin and gastrointestinal microbiota and are found regularly in up to 60% of healthy individuals. Previous fungal colonization is a necessary aspect to develop a Candida infection, and thus invasive disease is a result of an increment in this process, mainly due to either local or generalized immune impairment.[18,19]

The Critical Presentation of SARS-CoV-2 infection requires ICU management. Intensive-care-unit (ICU) patients are at risk of acquiring nosocomial infections, which could increase the mortality incidence in these patients. In SARS-CoV-2 infection, there is an important depletion of lymphocytes, and their subtypes like CD8+ and CD4+ T-cells[20-22] This phenomenon is the result of a dysregulated immune response by the virus that increases the immunosuppression. Also, this phenomenon can be associated with a high risk of secondary bacterial infection.[23] In patients with COVID-19 who have lymphopenia, it could be a predictor of progression and mortality, as it is also experienced by HIV patients. The neutrophils and monocytes/macrophages are important types of cells for host defense against Candida, but they are not affected by SARS-CoV-2,[24] suggesting that they are not responsible for candidemia.[25,26]

In our results, the mean lymphocyte count was 1,24 and 42% (9/21) had lymphopenia. However, the studied population presented a high number of risk factors traditionally related to candidemia. Some of the most important risk factors for this disease and its associated mortality are ICU admissions, prolonged hospital stays, invasive mechanical ventilation, use of antibiotics and steroids, and comorbidities such as diabetes mellitus. This correlates to Kullberg et al.,[10] Pappa et al.,[11] and Arastehfar et al.[23] research, where similar conditions associated with candidemia are described, in addition to abdominal surgery, pancreatitis, cancer, organ transplantation, and hemodialysis.

The use of corticosteroids has proven to be useful in the treatment of hospitalized COVID-19 patients.[27,28] Nonetheless, the administration of these drugs is a risk factor for mortality in patients with candidemia.[29,30] 76% of the subjects in our study had been submitted to steroid therapy, with a median length of treatment of 2.6days. The prescription of these immunomodulatory medications should be taken into consideration in patients with an increased risk for candidemia.[31,32]

Candida albicans was the most prevalent species, however, the incidence of other Candida species as etiologic is rising around the world, as in the last years many countries have reported an increase in infections associated with non-albicans.[33] In a study conducted, in Oman, five candidemia cases were reported and Candida albicans were identified in 4 of them.[34] In contrast, in a study from New Delhi, candidemia affected 15 critically ill coronavirus disease patients admitted to an ICU during April–July 2020, and Candida auris accounted for two-thirds of the cases.[35]

According to a recently published review, of all the invasive yeast infections found amongst critically ill COVID-19 patients C. albicans

(19/43; 44.1%) was shown to be the most prevalent yeast species, followed by Candida auris (10/43; 23.2%); Candida glabrata, Candida parapsilosis, Candida tropicalis, and S. cerevisiae (2/43; 4.6% each); and Candida krusei and Rhodotorula spp. (1/43; 2.3% each).[26,36,37] This correlates to our results, where Candida albicans is the most common etiology. In addition, we found two other species, Candida lipolytica and Candida spherica, which are not frequently described in the existing literature. The relevance of these two species lies in Saad J. Taj-Aldeen et al. research, which reported high mortality rates in patients with fungemia caused by rare fungal agents.[38]

A retrospective study conducted in a Turkish ICU found that susceptibility to antifungal treatment was similar in different yeast species. However, there was an important difference in incidence and steroid use in COVID-19 patients ($p<0.001$), resulting in higher mortality (92.5%). An interesting finding was that the delay of treatment was detrimental to prognosis, with a significant increase in mortality. Kayaaslan et al. state that candidiasis usually develops in the first two weeks of a hospital stay, demonstrating that detection is crucial.[14] In our study the median days to diagnosis was around three weeks, thus prevention and timely screening could prevent this complication.

Some studies manifest that although antifungal therapy can be effective, it does not reduce mortality in COVID-19 patients, owing to the fact of an earlier presentation, as well as disease potentiation. Such was the case in our study, where two-thirds of the subjects received therapy, which was mostly unsuccessful.[39,40]

Further and deeper studies are needed to ascertain the exact correlation between infections and the best measures to reduce morbidity and mortality. One of the limitations of our study was not following up on more accurate clinical and laboratory parameters since that data would have provided new insights into this topic. Moreover, difficulties such as laboratory overload due to the ongoing pandemic may have skewed times-to-result and therefore altered the outcomes of this study.

Conclusion

The relationship between COVID-19 and candidemia has not been established yet, however, this binomial has shown a significant increase in mortality. While SARS-CoV-2 remains be the focal point of most infectious disease practices, concomitant infections and factors that may aggravate COVID-19 should be considered in the hospital setting, especially in critical-care units. The high mortality in COVID-19 and candidemia-coinfected individuals has proven the relevance of assessing these patients promptly. This mortality could be associated to the delay in detection and treatment initiation.

It is imperative to develop predictive scores to facilitate the early diagnosis and consequential timely treatment of candidiasis, contributing to reduced mortality in these patients. It might be time to consider empiric antifungal therapeutics as a preventive measure in some specific patients with high risk.

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Conflicts of interest

The authors declare there is no conflict of interest.

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