The frequency of and risk factors for *Candida* fungemia

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Abstract

Objective: to describe the population of patients with candidemia, the risk factors for developing fluconazole-resistant candidemia, its frequency, and its 10-year distribution.

Materials and method: this was a multicenter retrospective cohort study enrolling patients with *Candida spp*. fungemia diagnosed between January 2010 and December 2020. Multivariate analysis was done using logistic regression to determine the risk factors associated with developing fungemia due to fluconazole-resistant species.

Results: there were 286 patients with *Candida spp*. fungemia; 19.9% of the isolates were fluconazole-resistant, and *C. albicans* was the most common species (38.8%). *C. glabrata* (26%), *C. krusei* (25%) and *C. tropicalis* (21%) predominated in the fluconazole-resistant group. Prior use of antifungals (OR 2.45; 95% CI 1.07–5.58; p = <0.033) and malnutrition (OR 2.34; 95% CI 1.11 – 4.65; p = 0.015) were independently related to the onset of fluconazole-resistant candidemia.

Conclusions: fungemia caused by non-*albicans Candida* species and fluconazole-resistant species has a high incidence and has been increasing over time. Prior use of antifungals is associated with developing fluconazole-resistant candidemia, as is malnutrition. This finding has not been reported in previous studies and warrants confirmation with further research. The effect of SARS-CoV-2 infection on the development of candidemias is well-known, and its actual impact on our population should be measured in future studies.
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Keywords: *Candidemia, drug resistance, fluconazole, risk factors, mortality*

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Introduction

Candida is the most common causal agent among opportunistic fungal infections, and its most serious manifestation is fungemia, which is a growing problem worldwide. *Candida* species are the most common cause of bloodstream infections in the United States (1), and one of the most frequently isolated germs in intensive care unit (ICU) patients in many countries (2). The mortality associated with these infections may be up to 40% (3). Over the last few decades, the incidence of this infection has increased significantly in critically ill patients, especially patients with prolonged ICU stays or those who have required invasive procedures such as central venous catheter placement, invasive mechanical ventilation, parenteral nutrition, hemodialysis, blood transfusions, prolonged antibiotic treatment and immunosuppressive treatment (4). Worldwide, the most frequently isolated species in patients with candidemia are *Candida albicans* (65.3%), *Candida glabrata* (11.3%), *Candida tropicalis* (7.2%), *Candida parapsilosis* (6.0%) and *Candida krusei* (2.4%) (5). However, this distribution may vary depending on the geographical area and even from one institution to another (6). In previous ICU studies in our setting, fungemias due to *C. albicans* species were the most frequent (43.6%), followed by *C. tropicalis* (23.4%) and *C. parapsilosis* (13.9%) (7).

Some studies have shown a higher frequency of invasive infections caused by azole-resistant *Candida species, with the main risk factors including* neutropenia, chronic kidney disease, prior exposure to fluconazole or antibiotic treatment, a history of gastrointestinal surgery, bone marrow transplantation and the neonatal age group (7, 8). Furthermore, the frequency of infections caused by non-albicans *Candida* (*C. glabrata* y *C. krusei) has increased*, which, in the context of the low susceptibility to antifungal agents shown by these germs, makes it even more difficult to select empirical treatment for this type of infections (9). This trend toward an increased incidence of non-albicans *Candida* infections

is a global phenomenon, associated not only with increased patient morbidity and mortality, but also with the need for longer antimicrobial therapy (10, 11).

Local studies show a high proportion of fluconazole resistance (11.3%) and dose-dependent susceptible isolates (10%) (12), higher than those reported in Europe, Asia, North America and other Latin American countries (6.2% resistant isolates and 3.6% dose-dependent susceptible isolates) (13). Furthermore, Colombia has the highest incidence of candidemia in Latin America (14), which also varies by geographical area within the country (15). The reasons for the high local frequency of candidemia and its resistance to azoles, as well as the epidemiological changes over the last few years in Colombia, are unclear. The objective of this study is to describe the population of patients with candidemia in the city of Medellín, as well as the risk factors for developing fluconazole-resistant candidemia in this setting. We also describe the frequency of fluconazole-resistant *Candida*, the change in this frequency and its distribution over 10 years (2010-2020).

Materials and method

Design, population and setting

A retrospective cohort study was performed at three of the main hospitals in Medellín, Colombia. All adult patients over the age of 18 who were hospitalized with candidemia documented by blood cultures between January 1, 2010, and December 31, 2020, were included. The candidemia episodes were found in the microbiology databases at each institution. Each patient's clinical and demographic information was obtained from the electronic medical charts at each hospital. Patients with positive *Candida cultures without candidemia, and those with isolates that did not have a fluconazole resistance profile or with isolates considered to be due to contamination during patient care were excluded. The selected patients were divided into two groups: patients with bloodstream infections caused by fluconozole-sensitive Candida* species versus fluconazole-resistant species. The STROBE guidelines were followed for the paper (16).

The patients' data were reviewed through the electronic medical chart system at the three hospitals and stored in the REDCap system. Baseline demographic data, comorbidities, the *Candida species, risk factors for candidemia, empirical antifungal treatment, definitive antifungal treatment, complications of candidemia* (shock, mechanical ventilation, dialysis and infectious seeding) and associated clinical outcomes (mortality, overall stay and ICU stay) were included. Malnutrition was defined as a body mass index (BMI) < 18.5 kg/m^2 or chronic use of total parenteral nutrition (TPN), and hematological malignancy was defined as the presence of leukemia, lymphoma or multiple myeloma.

Microbiology

Candida species isolates were obtained from blood cultures incubated for an average of 96 hours, although this period could be longer if there was a high clinical suspicion. The samples were processed at each hospital's reference laboratory; their fluconazole susceptibility was determined using the VITEK® 2 system. Minimum inhibitory concentrations (MICs) to determine sensitivity or resistance were based on the cut-off points established by the Clinical & Laboratory Standards Institute (CLSI) and the *European Committee on Antimicrobial Susceptibility Testing* (EUCAST) (6). *C. krusei* isolates were considered intrinsically resistant to fluconazole.

Statistical analysis

Frequencies and percentages were used for categorical variables. Quantitative variables were divided based on whether they were normally distributed or not, using the Shapiro-Wilk test. Variables with a non-normal distribution were shown as medians and interquartile range and were compared using the Mann-Whitney U test. Variables with a normal distribution were presented as means and standard deviation and were compared using Student's t-test. Statistical significance was defined as a two-tailed p value <0.05. A bivariate analysis was run in which the approximation used for categorical variables was the odds ratio (OR) and for continuous variables was the mean difference (MD). Variables with $p < 0.1$ after the first analysis were included in a multivariate logistic regression analysis to identify which were independently associated with fluconazole resistance. Data were analyzed using EpiDat version 4.2 (17).

Ethical considerations

The investigators adhered to the 2013 Declaration of Helsinki for human research. The project was approved by the ethics committees of the three participating institutions.

Results

Between 2010 and 2020, 286 patients with candidemia who met the inclusion criteria were found (Figure 1). The most common prior medical conditions included malnutrition (38.4%), solid organ cancer (16.8%), diabetes (16.1%), chemotherapy treatment (16.1%), hematological cancer (13.3%) and neutropenia (11.9%). Altogether, 85.7% of the patients had been exposed to antibiotics prior to developing candidemia and 37.8% had been exposed to glucocorticoids. The use of invasive devices was found in 249 patients (87.1%), 73.1% of which were removed after diagnosing candidemia. The remaining demographic characteristics and risk factors of the enrolled patients are shown in Table 1. A total of 57 candidemia cases (19.9%) had documented fluconazole resistance. The most frequent risk factors in the group of patients with fluconazole-resistant candidemia were malnutrition (52.6%), active chemotherapy (28%), hematological cancer (24%), solid organ cancer (19%) and diabetes (7%). In patients with fluconazole-sensitive candidemia, the most common risk factors were diabetes (17%), solid organ cancer (16%), chemotherapy (13%) and chronic kidney disease (12%); no comorbidities were found in 15% of the cases.

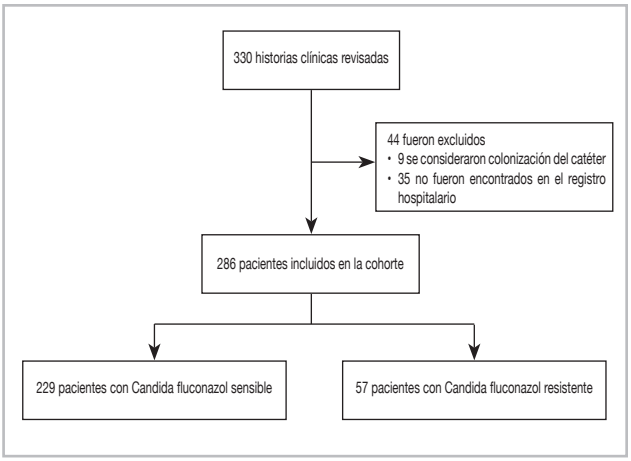

Figure 1. *Flowchart of the medical histories reviewed and patients included.*

C. albicans was responsible for 38.9% of the candidemia episodes, while non-albicans *Candida* species were responsible for the remaining 61.1%. The predominant *Candida* species in the fluconazole-resistant group were *C. glabrata* (26%), *C. krusei* (25%) and *C tropicalis* (21%). In patients with fluconazole-sensitive candidemia, the most frequently isolated *Candida* species was *C. albicans* (45%), followed by *C. tropicalis* (28%) and C. *parapsilosis* (15%). The complete distribution of *Candida* species according to sensitivity can be found in Figure 2.

A growing trend in candidemias was found over time, with peaks between 2019 and 2020 (Figure 2a). This increase was due to both *C. albicans* and non-albicans Candida candidemias (Figure 2b). The proportion of fluconazole-resistant isolates varied, accounting for 5 to 28% of all candidemia episodes annually (Figures 2c and 2d).

The onset of candidemia due to fluconazole-resistant species was more likely in patients with hematological cancer (OR 1.78; 95% CI 1.33–5.8; p = <0.001), those on active chemotherapy (OR 3.42; 95%, CI 1.67–6.99; p = <0.001), in malnourished patients (OR 2.06; 95% CI 1.15-3.72; p = 0.01), in patients who had previously received antifungal treatment (OR 3.29; 95% CI 1.75–6.19; p = <0.001) and in those who had received prior transfusions (OR 1.91; 95% CI 1.04–3.51; p = <0.035). On the other hand, fluconazole-resistant candidemia was less likely in patients who did not have any comorbidities (OR 0.3; 95% CI 0.07–0.95; p

Table 1. *Risk factors associated with fluconazole-resistant candidemias.*

Characteristics	*Resistant Candida* (n=57)	Sensitive *Candida* (n= 229)	OR (95% CI)	P value
History (%)				
Solid organ transplant	5 (8.77)	10 (4.37)	2.10 (0.69-6.42)	0.31
Diabetes mellitus	7 (12.28)	39 (17.03)	0.68 (0.28-1.62)	0.50
Solid organ cancer	11 (19.30)	37 (16.16)	1.24 (0.58-2.61)	0.55
Hematological cancer	14 (24.56)	24 (10.48)	2.78 (1.33 – 5.8)	<0.001
HIV infection	1 (1.75)	4 (1.75)	1 (0.11-9.16)	1
Chronic kidney disease	4 (7.02)	29 (12.66)	0.52 (0.17 – 1.54)	0.33
Liver disease	3 (5.26)	16 (6.99)	0.73 (0.20 – 2.63)	0.86
Neutropenia	10 (17.54)	24 (10.48)	1.81 (0.81-4.05)	0.21
Chemotherapy	16 (28.07)	30 (13.10)	3.42 (1.67-6.99)	<0.001
Radiation therapy	2 (3.51)	5 (2.18)	1.62 (0.3-8.62)	0.91
Autoimmune diseases	3 (5.26)	16 (6.99)	0.73 (0.2 – 2.63)	0.86
Malnutrition	30 (52.6)	80 (34.9)	2.06 (1.15-3.72)	0.01
None	ww3 (5.26)	35 (15.28)	0.3 (0.07-0.95)	0.046
Medications and procedures * (%)				
Prior steroids	24 (42.11)	84 (36.68)	1.25 (0.69 – 2.26)	0.54
Prior antibiotics	51 (89.47)	194 (84.72)	1.53 (0.61-3.84)	0.48
Prior antifungal agents	23 (40.35)	39 (17.03)	3.29 (1.75-6.19)	<0.001
Hemodialysis	8 (14.04)	60 (26.20)	0.45 (0.19-0.99)	0.05
Invasions (%)				
Central venous catheter	42 (73.68)	170 (74.24)	0.97(0.5-1.87)	1
Mechanical ventilation	9 (15.79)	45 (19.65)	0.76 (0.35-1.67)	0.63
Urinary catheter	19 (33.33)	91 (39.74)	0.75 (0.41-1.39)	0.46
Hemodialysis catheter	9 (15.79)	49 (21.40)	0.68 (0.31-1.50)	0.44
Abdominal surgery	21 (36.84)	90 (39.30)	0.9 (0.49-1.64)	0.85
Parenteral nutrition	22 (38.60)	74 (32.31)	1.31 (0.72-2.4)	0.45
Transfusion	38 (66.67)	117 (51.09)	1.91(1.04-3.51)	0.035

**Four weeks prior to diagnosis (%).*

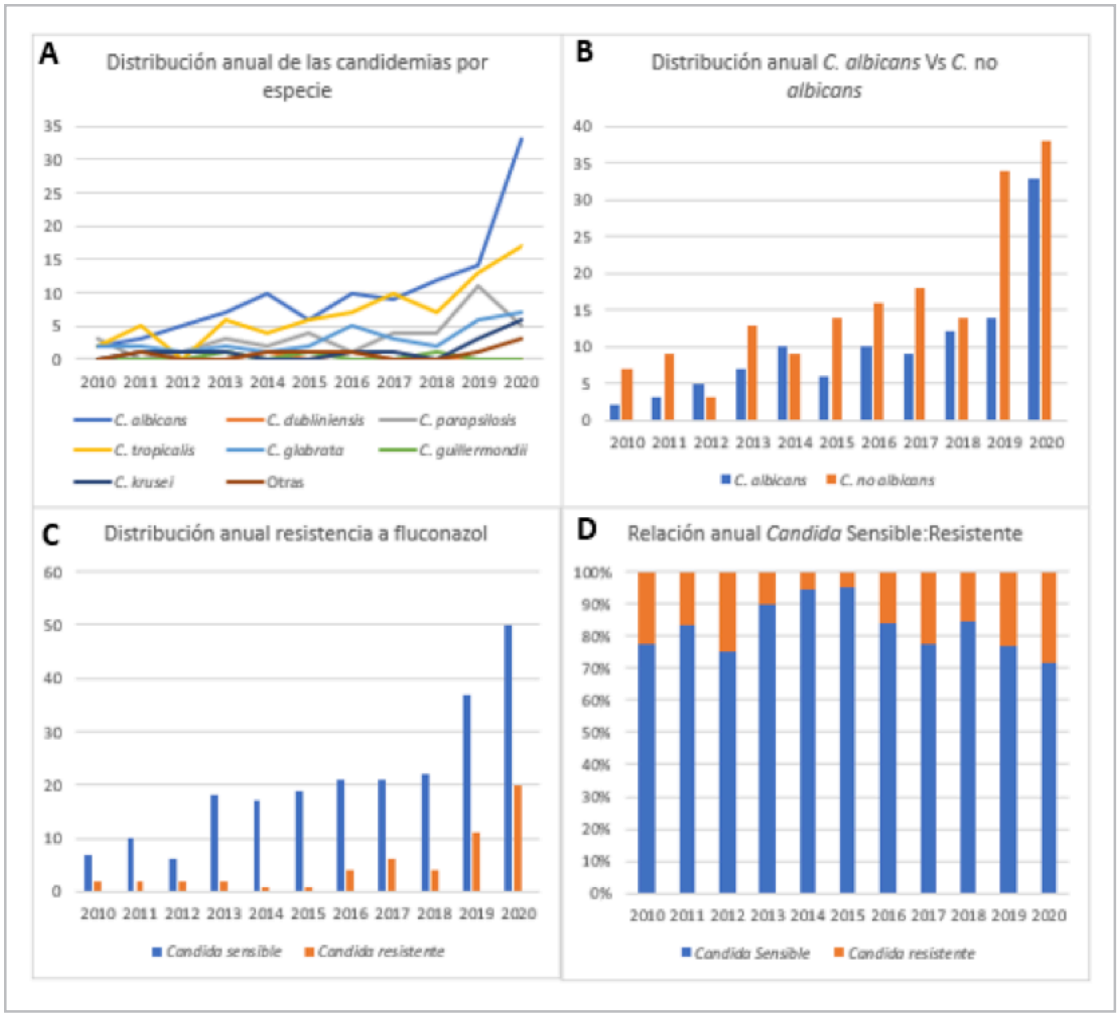

Figure 2. *Distribution of the candidemias.*

= 0.046) as well as in patients on hemodialysis (OR 0.45; 95% CI 0.19–0.99; p = 0.05).

The group with fluconazole-resistant candidemia had a 49% mortality rate versus 46% in the group with candidemia due to sensitive species, with no statistically significant differences (OR 1.13; 95% CI 0.63–2.04; p = 0.65). There were no differences, either, between the two groups with regard to the total days on antibiotics, length of stay in the special care unit (SCU) or ICU, or days elapsed to fungemia recurrence. However, there was a trend towards earlier fungemia recurrence in patients with resistant Candida species (mean difference [MD] -1.7; 95% CI -3.5–0.03; p = 0.05). Patients with fluconazole-resistant *Candida* had an average of 5.8 days of mechanical ventilation associated with the candidemia and 2.3 days of vasopressor use, which was less than that of patients with fluconazole-sensitive candidemia (MD -6.9; 95% IC -11.6 to -2.); p= 0.005; MD -2.5; 95% IC -4.2 to -0.8; p= 0.004, respectively). Other comparative outcomes between the groups with *Candida albicans* and non-albicans Candida fungemia are presented in Table 2.

In the multivariate analysis for factors associated with developing fluconazole-resistant candidemia, a history of malnutrition and prior antifungal use were independently associated with a higher risk (Table 3). Over 10 years (2010-2020), there was a documented increase in the frequency of *Candida, non-albicans Candida* and fluconazole-resistant *Candida* infections (Figure 2).

Discussion

The frequency of candidemia has been increasing (18) and is associated with high morbidity and mortality (19). Local reports indicate that *Candida* species are the sixth most common organism isolated in the ICU, accounting for 7% of all isolates. The most frequently isolated species are *C. albicans* (43.6%), followed by *C. tropicalis* (22.3%) and the *C. parapsilosis* complex (15.0%); these data are concordant with other local and national studies (12).

Large multicenter and international studies indicate that the incidence of the isolated Candida species varies significantly depending on the setting and geography. In one of

Table 2. *Outcomes of patients with fluconazole-resistant candidemia.*

Characteristics (%)	Resistant Candida group (n=57)	Sensitive Candida group (n= 229)	OR (95% CI)	P value
Post-candidemia shock	25 (44)	108 (47)	0.37 (0.48-1.57)	0.65
Candidemia recurrence	9 (16)	30 (13)	1.24 (0.52-2.74)	0.59
Post-candidemia dialysis	10 (17)	63 (27)	0.56 (0.25-1.15)	0.12
Presence of seeding	12 (21)	33 (14)	1.58 (0.73-3.26)	0.21
Mortality	28 (49)	105 (46)	1.13 (0.63-2.04)	0.65
Need for mechanical ventilation	21 (37)	110 (48)	0.63 (0.34 – 1.14)	0.12
Characteristics	**Resistant Candida group**	**Sensitive Candida group**	**Differnce in means (95% CI)**	**P value**
Days on antifungals	(n = 51) 26.5 ± 29.7	(n = 207) 20.4 ± 28.0	6.0 (-3.1 a 15.2)	0.19
Days in ICU	(n = 57) 14.2 ± 23.2	(n = 229) 17.6 ± 29.1	-3.3 (-10.5 a 3.8)	0.35
Days in SCU	(n = 57) 2.6 ± 4.3	(n = 229) 3.7 ± 8.0	-1.0 (-2.6 a 0.4)	0.16
Length of hospitalization	(n = 57) 56.4 ± 43.8	(n = 229) 45.1 ± 46.1	11.1 (-1.8 a 24.1)	0.09
Days on vasopressors	(n = 23) 2.3 ± 3.0	(n = 116) 4.9 ± 6.1	-2.5 (-4.2 a -0.8)	0.004
Days on mechanical ventilation	(n = 21) 5.8 ± 6.6	(n = 117) 12.7 ± 20.7	-6.9 (-11.6 a -2.1)	0.005
Days to recurrence	(n = 12) 3.5 ± 1.9	(n = 29) 5.3 ± 3.7	-1.7 (-3.5 a 0.03)	0.05

Table 3. *Multivariate analysis of the risk factors associated with resistant candidemia.*

Variable	OR	95% CI	P value
Prior transfusion	1.65	0.84 – 3.26	0.145
Use of chemotherapy	1.90	0.66 – 5.50	0.233
Malnutrition	2.34	1.11 – 4.65	0.015
No comorbidities	0.41	0.11 – 1.46	0.173
Prior use of antifungals	2.5	1.28 – 4.89	0.007
Hematological cancer	2.0	0.64 – 6.25	0.232

these studies, the most common isolates were *C. albicans* (65.3%), followed by *Candida glabrata* (11.3%), *Candida tropicalis* (7.2%), *Candida parapsilosis* (6.0%) and *Candida krusei* (2.4%) (13), 6.2% of which were resistant and 3.6% dose-dependent susceptible, which contrasts with the local epidemiology, in which the proportion is much higher (11.3 and 10%, respectively) (12).

In our study, as in the local epidemiology, the most commonly isolated species was C. albicans (38.8%), followed by *C. tropicalis* (22.3%) and the *C. parapsilosis complex* (15.0%). In addition, there were 19.9% resistant strains, much higher than what has been reported both locally and globally. Candidemia due to fluconazole-resistant species was more likely in patients with hematological cancer, those on active chemotherapy, malnourished patients, patients who had received prior antifungal treatment and those who had received prior blood transfusions.

Fungemias due to non-albicans Candida species are also associated with higher morbidity, mortality, treatment failure and costs (20-22). Although *C. albicans* is the most commonly reported isolate in some studies (23–26), this has been changing over the last few years (11, 27–29), with increasingly greater proportions of non-albicans Candida isolates (9, 23). Despite *C. albicans* being historically reported as the most frequent isolate in Colombia (30), our study shows a higher representation of non-albicans *Candida at* 61%. This could be due to the fact that the hospitals from which the cohort patients were selected are regional referral centers for gastrointestinal surgery, intestinal rehabilitation and hematology-oncology, which could be associated with a higher use of fluconazole as empirical therapy to treat some of the complications of these conditions. All of these are risk factors described for developing candidemia due to non-albicans *Candida* (31).

In another vein, our study showed a progressive increase in the frequency of candidemias beginning in 2010, with a marked rise between 2019 and 2020. We hypothesize that the marked rise after 2010 is due to a progression toward referral centers with greater operational capacity in the previously described areas, which implies more patients with more risk factors for developing candidemias (higher Acute Physiology and Chronic Health Evaluation II [APACHE II] scores, more abdominal surgeries, and greater use of antibiotics, central catheters, and TPN, among others). The marked increase in cases over the last two study years is probably explained by the association between invasive fungal infections and COVID-19 (32,33), with reports of up to 25% of candidemias preceded by this viral infection (33).

Fluconazole-resistant *Candida* infections are also associated with more adverse outcomes. The literature reports

azole resistance rates between 2.3 and 14.3%, depending on the *Candida* species (27). Our study found a higher frequency (19.9%). This increased frequency has been found in populations with high rates of non-albicans *Candida* isolation (21, 35), as in our study (61%), where *C. tropicalis* and *C. glabrata* isolates (which are more resistant) were also more frequently detected. This correlates with contemporary cohorts in which non-albicans Candida candidemia represents 20 to 60% of the isolates (21,35,36), with *C. parapsilosis* and *C. glabrata* as frequent as 37 and 59% of candidemias, respectively (30, 33).

We found a high frequency of resistance in *C. parapsilosis* (30%), a finding which, while unusual (34), has been increasing in some reports (11, 35). This phenomenon is believed to be secondary to exposure to fluconazole which induces an overexpression and mutation of genes like *ERG11, which code for azole efflux pumps* (36). These same azole-resistance mechanisms have been found to be involved in other *Candida species*, in which overexpression of other genes like CDR1 (*Candida drug resistance gene*) and MDR1 (*multidrug resistance gene*) has also been reported (37–39). As described in other studies (27, 37, 38), in our cohort, the prior use of antifungal agents was associated with a higher risk of fluconazole-resistant candidemia.

To our knowledge, this cohort is the first to show the association between malnutrition and the risk of developing fluconazole-resistant candidemia. This result is not explained by the higher prevalence of malnutrition in patients with hematological cancer or on chemotherapy, as these variables were not independently associated with an increased risk. Malnutrition has previously been described as a risk factor for developing *C. krusei candidemias (40). To control for this confounding factor, a new multivariate analysis was run excluding C. krusei* candidemias (Supplementary Table 1), in which the association between malnutrition and fluconazole-resistant candidemia continued to be significant.

Malnutrition has been found to be associated with decreased phagocytosis, a lower concentration of IL-2 (41), immunosuppressive states (42), an increased risk of nosocomial infections (43-45) and negative outcomes in patients with candidemia (40, 46, 47). Based on this, we propose the hypothesis that malnutrition behaves as a risk factor for fluconazole-resistant candidemia, as this infection is almost exclusively nosocomial, and macrophage- and IL-2-mediated phagocytosis affects its immune control (48, 49).

Supplementary Table 1. *Multivariate analysis of the risk factors associated with resistant candidemia, excluding candidemias due to C. krusei..*

Variable	OR	95% CI	P value
Use of chemotherapy	2.4	0.74 – 7.88	0.14
Malnutrition	2.21	1.02 – 4.39	0.04
No comorbidities	0.51	0.28 – 3.91	0.3
Prior use of antifungals	1.99	0.94 – 4.22	0.07
Hematological cancer	1.06	0.28 – 3.91	0.9

Furthermore, a strong association has been found between candidemia, immunosuppression (50, 51) and malnutrition, which, in turn, worsens outcomes (40, 46, 47).

Regarding the strengths of the study, it is important to highlight that this was a multicenter study at institutions with different emphases and with a patient sample comparable to that of other large studies around the world (7, 11, 12, 22). As for its limitations, the study measured overall inpatient mortality rather than 14 and 30-day mortality, which makes it difficult to analyze this outcome, and could promote bias. The retrospective nature of the study prevents an evaluation of all risk factors and could introduce measurement bias. In addition, neither the time elapsed from candidemia diagnosis to antifungal treatment, nor the APACHE II score were recorded, which are directly correlated with the risk of mortality. Finally, given that the study was designed and started prior to 2019, SARS-CoV-2 infection was not included as a comorbidity.

Conclusion

We found a high frequency of non-albicans Candida and fluconozole-resistant Candida fungemias, which have been increasing over the last few years, especially since 2019. *C. glabrata* was found to be the main cause of fluconazole-resistant candidemia. There was no statistically significant difference in mortality throughout the hospital stay in fluconazole-sensitive versus resistant candidemias, but fluconazole-resistant candidemias were associated with less time on vasopressor and inotropic support.

In addition, prior use of antifungal agents and malnutrition were identified as independent risk factors for developing fluconazole-resistant candidemia. We highlight the latter as a new finding that merits confirmation with further studies. The effect of SARS-CoV-2 infection on the development of candidemias is well-known, and its actual impact on our population should be measured in subsequent studies.

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