Prognostic factors of *Candida* spp. bloodstream infection in adults: A nine-year retrospective cohort study across tertiary hospitals in Brazil and Spain

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Summary

Background Mortality rates among adults with candidemia vary widely in different geographical settings. Studies directly comparing epidemiology and clinical practices between countries are scarce and could bring insights into improving clinical outcomes.

Methods Retrospective cohort including adults with candidemia diagnosed in five tertiary hospitals from Brazil and Spain between 2010-2018. Adequate therapeutic management included appropriate antifungal therapy and central-venous-catheter (CVC) removal within 48 h of fungemia. Primary endpoints were mortality rates at 14 and 30 days. Secondary endpoints were prognostic factors associated with 30-day mortality.

Findings Overall, 720 patients were included, being 323 from Spain. Spanish patients received echinocandins more often (52·5% vs. 39·3%, $p = 0.001$), initiated antifungals earlier [2 (0-7) vs. 2 days (0-16), $p<0.001$], and had faster CVC-removal [1 (0-42) vs. 2 days (0-38), $p = 0.012$]. Mortality was higher among Brazilians at 14 days (35·8% vs. 20·1%, $p<0.001$), and at 30 days (51·9% vs. 31·6%, $p < 0.001$). Factors associated with mortality included: age [OR 1·02, 95%CI (1·008-1·032), $p = 0·001$], neutropenia [OR 3·24, 95%CI (1·594-6·585), $p = 0·001$], chronic pulmonary disease [OR 2·26, 95%CI (1·495-3·436), $p < 0·001$], corticosteroids [OR 1·45, 95%CI (1·018-2·079), $p = 0·039$], Pitt-Score>1 [OR 2·56, 95%CI (1·776-3·690), $p < 0·001$], and inadequate therapeutic management [OR 2·84, 95%CI (1·685-4·800), $p < 0·001$]. Being from Spain [OR 0·51, 95%CI (0·359-0·726), $p < 0·001$] and *C. parapsilosis* [OR 0·36, 95%CI (0·233-0·568), $p < 0·001$] were protective.

Interpretation Higher mortality rates were observed in Brazil. Factors associated with 30-day mortality included mainly epidemiological characteristics and inadequate therapeutic management. Thus, effective and prompt antifungals combined with CVC-removal still need to be emphasized in order to improve the prognosis of adults with candidemia.

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Research in context

Evidence before this study

Candidemia remains the most prevalent invasive fungal infection in hospital settings, culminating in high morbidity and mortality. Mortality rates among adults diagnosed with candidemia vary widely in different geographical settings, mainly due to differences in population at greater risk, and infection management. Real life studies with a direct comparison of epidemiology and therapeutic practices between countries are scarce and could bring more specific insights into improving clinical outcomes.

Added value of this study

The current study makes a direct comparison between tertiary hospitals from Brazil and Spain, which are countries with very distinct previously published mortality rates among adults with candidemia. Analyses sought to confirm those rates and to determine independent factors associated with mortality in order to identify areas of improvement. Our findings indicate that besides expected epidemiological differences, mortality was strongly associated with current inadequate therapeutic management and was highest where the choice for effective antifungal and source control were either not made or delayed.

Implications of all the available evidence

We addressed important drawbacks in real life practice, showing that well-known basic therapeutic cornerstones for candidemia such as early initiation of antifungals and prompt source control still represent a major challenge and need to be improved. Faster diagnostic methods and feasible evidence-based bundles of care supported by antifungal stewardship teams along with continuous medical education projects are warranted.

1. Introduction

Bloodstream infections by *Candida* species are the leading invasive mycosis in health care settings, conferring high rates of morbidity and mortality among hospitalized patients worldwide [1–6]. Prognostic factors associated with mortality have been studied and may change according to the geographic region due to differences in population at greater risk, species distribution, and infection management [2,4,5]. Yet, studies comparing the natural history of candidemia in settings with different economic backgrounds are scarce.

Despite advances in the field, previous studies suggest a higher global incidence of candidemia as a result of demographic changes and more complex invasive medical procedures [2,5]. Nevertheless, surveillance data varies considerably between countries, with reported incidence per 1,000 admissions of up to 2·5 cases in Brazil compared to 0·76 in Spain [7,8].

Moreover, mortality rates are also notably higher in Latin American countries when compared to Western Europe [2,9], reaching as high as 58·9% in a recent 21-year series of candidemia in Brazil compared to 20·2% in a multicentre study from Spain [7,10]. Unfortunately, particularly in Brazil, trends in mortality have barely changed over the last twenty years [2,10].

Contributing factors for such discrepancies have been suggested, including insufficient health care education and infection control, as well as differences in prophylactic and empirical practices [8,9,11]. However, no direct comparison between these settings has been made to provide insights into improving the overall clinical outcomes of adults with candidemia.

We aimed to compare the epidemiological profile, susceptible populations, aetiology, modifiable therapeutic practices, and clinical outcomes between public tertiary hospitals in Brazil and Spain in order to identify areas of improvement and investigate the underlying factors that may contribute to such prognostic variability.

2. Methods

2.1. Study design, population and setting

Retrospective cohort study including all adult patients ≥ 18 years of age with a peripheral blood culture yielding a *Candida* species diagnosed at five public tertiary hospitals participating in epidemiological studies in Brazil and Spain from January 2010 to December 2018.

A pre-established protocol with a dictionary of terms was fulfilled by a trained medical investigator for each patient in each centre with medical history and laboratory information retrieved up to 30 days from index candidemia. Only compatible and consistent data available in both countries' protocols were included in this study. Data included demographics, comorbidities, department of admission at diagnosis, risk factors for candidemia [2], Pitt-Score calculated at the onset of candidemia [12] for clinical severity, *Candida* species, antifungal choice and time of treatment initiation, time to central venous catheter (CVC) removal, complementary screening (ophthalmoscopy and echocardiography), complications (ocular candidiasis or endocarditis), and clinical outcomes at 14 and 30 days from index candidemia. No eligible patients had to be excluded due to missing data.

2.2. Definitions

Candidemia was defined as the isolation of *Candida* species from at least one peripheral blood culture. The date of the index candidemia was defined as the date the first positive blood culture for a *Candida* species was collected. Adequate therapeutic management was defined as the initiation of an effective antifungal drug [13] combined with catheter removal within 48 h from index candidemia. Severe cases were defined as those with a

Pitt-Score >1. Early CVC removal was noted when performed within 48 h from the extraction of the first positive blood culture, whereas late CVC removal was defined if obtained after 5 days from index candidemia. Early mortality occurred within 14 days from index candidemia, whereas late mortality was observed within 30 days.

2.3. Microbiology

In Brazil, along the first period of the study, isolates were identified at species level in the Reference Lab (Escola Paulista de Medicina, UNIFESP) by using microscopic morphology along with biochemical tests using the ID32C system (BioMérieux AS, Marcy [Etoile, France]. Likewise, *Candida* species were identified by classical phenotypical methods in Spain, combined with Matrix Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) in the later years in both countries.

2.4. Data analysis

We compared cases of candidemia in adult patients from public tertiary hospitals in Brazil and Spain in terms of epidemiology, clinical presentation, therapeutic practices, and outcomes. All-cause mortality at 14 and 30 days from the diagnosis was our primary endpoint. Secondary endpoints were prognostic factors associated with all cause 30-day mortality. All data available was collected by local investigators using a standard clinical form complemented by a dictionary of terms. Data was summarized using descriptive statistics. Categorical variables were reported as counts (%) and compared using either Fisher's exact test or chi-square test, as appropriate. Quantitative variables with a normal distribution were reported as mean ± standard deviation (SD) and compared using the Student's *t* test. Those with a non-normal distribution were described as median and interquartile range (IQR) and compared using the Mann Whitney *U*-test. Statistical significance was set at a two-tailed *p*-value <0·05. Variables of interest selected from the univariate analyses for each country with a *p*-value <0·1 were included in the initial multivariate logistic regression for independent prognostic factors associated with all-cause 30-day mortality after testing for interaction terms and adjusting for between-country differences. Non-significant variables were then excluded one by one in order of significance through the backwards method for the final model. Analyses were performed using SPSS V24 software package (SPSS Inc., Chicago, IL, USA).

2.5. Ethics approval

This study was approved by the respective institutional ethics committees in Spain (Comité Ético de Investigación Clínica del Hospital General Universitario Gregorio Marañón [CEIC-A1], study code MICRO.HGUGM.2015-071), and in Brazil (Comitê de Ética em Pesquisa [CEP] da Unifesp, study code 44989021.9.1001.5505).

2.6. Role of the funding source

Funding sources had no role in study design, data collection, data analysis, interpretation or writing of the present report.

3. Results

3.1. Epidemiology and clinical manifestations

A total of 720 adult patients with candidemia were included, being 397 from Brazil. Baseline characteristics of both groups are summarized in Table 1. Briefly, Spanish patients were slightly older [65·5 (23-87) vs. 64 years (18-97) $p = 0·003$], presented more solid cancer (50·2% vs. 28·7%, $p < 0·001$), and a surgical profile with previous abdominal surgery more often (36·2% vs. 26·4%, $p = 0·006$), whereas Brazilian patients had higher rates of renal insufficiency (42·7% vs. 22·0%, $p < 0·001$), developed a more severe clinical presentation (Pitt-Score >1 in 67·3% vs. 35·6%, $p < 0·001$), and were more likely to be at an intensive care unit at the time of diagnosis (46·9% vs. 21·1%, $p < 0·001$).

3.2. Microbiology

The distribution of *Candida* species was similar in both countries (Table 2), except for *Candida tropicalis*, which was more prevalent in Brazil (17·6% vs. 9·3%, $p = 0·002$).

3.3. Therapeutic management

General therapeutic practices are described in Table 3 and clinical management in cases from intensive care is shown in Table 4. Echinocandins were more frequently used to treat Spanish patients at some point during the candidemia episode (52·5% vs. 39·3%, $p = 0·001$). Nevertheless, they were mostly not the initial drug of choice neither in Spain, nor in Brazil (33·3% vs. 29·6%, $p = 0·340$) as was fluconazole in both countries (60·9% vs. 58·5%, $p = 0·566$), respectively. Although differences in time to antifungal initiation did not reach statistical significance among ICU patients in Spain or Brazil [2 days (0-6) vs. 2 (0-16), $p < 0·07$], the overall antifungal initiation and CVC removal were both performed earlier among Spanish when compared to Brazilian patients [2 days (0-7) vs. 2 (0-16), $p < 0·001$] and [1 day (0-42) vs. 2 (0-38), $p = 0·012$], respectively. Moreover, complementary screening was more frequently performed among the Spanish with ophthalmoscopy in 68·4% vs. 22·3%, $p < 0·001$, and echocardiogram in 75·2% vs. 41·1%, $p < 0·001$.

Variables Demographics and hospitalization	Total (n=720)	Brazil (n=397)	Spain (n=323)	*p*-value
Age (years), median (IQR)	66 (18-98)	64 (18-97)	65.5 (23-87)	0.003
Gender (male), n (%)	411 (57.1)	200 (50.4)	211 (65.3)	<0.001
Time from admission to index candidemia, median in days (IQR) ICU admission at diagnosis, n (%)	19 (0-387) 254 (35.3)	19 (0-387) 186 (46.9)	20 (0-229) 68 (21.1)	0.514 <0.001
Comorbidities, n (%)				
Cardiovascular disease	183 (25.4)	78 (19.6)	105 (32.5)	<0.001
Lung disease	147 (20.4)	76 (19.2)	71 (22.0)	0.403
Kidney failure	240 (33.4)	169 (42.7)	71 (22.0)	<0.001
Diabetes mellitus	186 (25.9)	100 (25.4)	86 (26.6)	0.732
Neurological disorder	172 (23.9)	93 (23.4)	79 (24.5)	1
Chronic liver disease	89 (12.4)	48 (12.1)	41 (12.7)	0.821
Gastrointestinal disease	65 (9.0)	9 (2.3)	56 (17.3)	<0.001
Solid cancer	276 (38.3)	114 (28.7)	162 (50.2)	<0.001
Hematological malignancy	40 (5.6)	28 (7.1)	12 (3.7)	0.071
Bone marrow transplant	18 (2.5)	10 (2.5)	8 (2.5)	1
Solid organ transplant	26 (3.6)	16 (4.0)	10(3.1)	0.552
HIV	14 (2.7)	1 (0.5)	13 (4.0)	0.022
Associated conditions, n (%)				
Chemotherapy	90 (12.5)	27 (6.8)	63 (19.5)	<0.001
Neutropenia (<500 cells/μL)	43 (6.0)	24 (6.1)	19 (5.9)	1
Abdominal surgery*	222 (30.8)	105 (26.4)	117 (36.2)	0.006
Total parenteral nutrition	264 (36.7)	81 (20.4)	183 (56.7)	<0.001
CVC at place	559 (77.6)	329 (82.9)	265 (82.0)	0.844
Antibiotic use**	608 (84.4)	314 (79.1)	294 (71.0)	<0.001
Antifungal use**	143 (19.9)	69 (17.5)	74 (22.9)	0.075
Corticosteroids	261 (36.5)	165 (42.0)	96 (29.7)	0.001
Other immunosuppressives	87 (12.2)	57 (14.5)	30 (9.3)	0.038

***Table 1*: Baseline characteristics of candidemic adults diagnosed at tertiary public hospitals in Brazil vs. Spain from 2010 to 2018.**
ICU: intensive care unit; HIV: human immunodeficiency virus; CVC: central venous catheter. *Previous three months. **Previous month.

Variables *Candida* species/complex species, n (%)	Total (n=720)	Brazil (n=397)	Spain (n=323)	*p*-value
C. albicans	327 (45.4)	173 (43.6)	154 (47.7)	0.292
C. parapsilosis complex	150 (20.8)	79 (19.9)	71 (22.0)	0.519
C. glabrata	102 (14.2)	51 (12.8)	51 (15.8)	0.283
C. tropicalis	100 (13.9)	70 (17.6)	30 (9.3)	0.002
C. krusei	16 (2.2)	7 (1.8)	9 (2.8)	0.448
C. guilliermondii complex	8 (1.1)	5 (1.3)	3 (0.9)	0.737
Other *Candida* spp.	12 (1.7)	1 (0.3)	11 (3.4)	0.001

***Table 2*: Microbiological characteristics of 720 adult patients with candidemia diagnosed at 5 tertiary public hospitals in Brazil vs. Spain from 2010-2018.**

3.4. Clinical outcomes

Clinical outcomes regarding complications such as chorioretinitis, endocarditis, and all-cause mortality at 14 and 30 days from fungemia are described in Table 5. Mortality rates were higher in the Brazilian cohort both at 14-days (35·8% vs. 20·1%, $p < 0·001$) and at 30-days

Variables Antifungal therapy, n (%)	Brazil (n=397)	Spain (n=323)	*p*-value
No antifungals prescribed	79 (19.9)	24 (7.4)	<0.001
Echinocandin as initial treatment	94/318 (29.6)	100/299 (33.4)	0.340
Echinocandin at any time during the episode	125/318 (39.3)	157/299 (52.5)	0.001
Time to initial treatment, median in days (IQR)	2 (0-16)	2 (0-7)	<0.001
Infection source control, n (%)			
Early CVC removal*	148/321 (46.1)	128/232 (55.2)	0.039
Late CVC removal**	73/321 (22.7)	32/232 (13.8)	0.008
CVC removal at any time during the episode	304/321 (94.7)	209/232 (90.1)	0.046
Time from initial antifungal to CVC removal, median in days (IQR)	2 (0-38)	1 (0-42)	0.012
Inadequate AF treatment***	322 (81.1)	205 (63.5)	<0.001
Complementary screening, n (%)			
Ophthalmoscopy	45/202 (22.3)	221/323 (68.4)	<0.001
Echocardiogram	83/202 (41.1)	243/323 (75.2)	<0.001

***Table 3*: Overall therapeutic management of 720 adults with candidemia diagnosed at 5 tertiary public hospitals in Brazil *versus* Spain from 2010-2018**

*Within 48 h from the extraction of the first positive blood culture. **After 5 days from the extraction of the first positive blood culture. ***Patients without effective antifungal and CVC removal both within 48 h from index candidemia. AF: antifungal.
Denominators are used when the number of patients is different from the whole sample indicated at the top of the column.

Variables	Brazil (n=186)	Spain (n=68)	*p*-value
Antifungal therapy, n (%)			
No antifungals prescribed	34 (18.3)	5 (7.4)	0.048
Echinocandin as initial treatment	46/152 (30.3)	37/63 (58.7)	<0.001
Echinocandin at any time during the episode	60/152 (39.5)	46/63 (73.0)	<0.001
Time to initial treatment, median in days (IQR)	2 (0-16)	2 (0-6)	0.07
Infection source control, n (%)			
Early CVC removal*	86/170 (50.6)	37/58 (58.0)	0.094
Late CVC removal**	36/170 (21.2)	3/58 (5.2)	0.008
CVC removal at any time during the episode	163/170 (95.9)	52/58 (90.1)	0.1
Time from initial antifungal to CVC removal, median in days (IQR)	2 (0-38)	1 (0-17)	0.012
Inadequate therapeutic management***	143 (76.9)	35 (51.5)	<0.001
Complementary screening, n (%)			
Ophthalmoscopy	16/96 (16.7)	46/68 (67.6)	<0.001
Echocardiogram	39/96 (40.6)	47/68 (69.1)	<0.001

***Table 4*: Intensive care therapeutic management of adults with candidemia diagnosed at 5 tertiary public hospitals in Brazil *versus* Spain from 2010-2018**

*Within 48 h from the extraction of the first positive blood culture. **After 5 days from the extraction of the first positive blood culture.
*** Patients without effective antifungal and CVC removal both within 48 h from index candidemia.
Denominators are used when the number of patients is different from the whole sample indicated at the top of the column.

from index candidemia (51·9% vs. 31·6%, $p < 0·001$), even among patients with lower Pitt-Scores (Table 5).

3.5. Prognostic factors of mortality in Candidemia

Independent factors associated with all-cause 30-day mortality are described in the final model of Table 6, including: age [OR 1·02, 95%CI (1·008-1·032), $p = 0·001$], neutropenia [OR 3·24, 95%CI (1·594-6·585), $p = 0·001$], chronic pulmonary disease [OR 2·26, 95%CI (1·495-3·436), $p < 0·001$], corticosteroids [OR 1·45, 95%CI (1·018-2·079), $p = 0·039$], Pitt-Score>1 [OR 2·56, 95%CI (1·776-3·690), $p < 0·001$], and inadequate therapeutic management [OR 2·84, 95%CI (1·685-

Variables	Brazil (n=397)	Spain (n=323)	*p*-value
Complications*, n (%)			
Ocular candidiasis	2/45 (4.4)	31/221(14.0)	0.085
Endocarditis	7/83 (8.4)	7/243 (2.9)	0.053
General			
14-day mortality	142 (35.8)	65 (20.1)	<0.001
30-day mortality	206 (51.9)	102 (31.6)	<0.001
Pitt Score ≤1			
14-day mortality	41/130 (31.5)	33/208 (15.9)	0.001
30-day mortality	64/130 (49.2)	56/208 (26.9)	<0.001
Intensive Care			
14-day mortality	88/186 (47.3)	15/68 (22.1)	<0.001
30-day mortality	121/186 (65.1)	27/68 (39.7)	<0.001

***Table 5*: Clinical outcomes of 720 adults with candidemia diagnosed at tertiary public hospitals in Brazil and Spain from 2010-2018,**
*Percentages were calculated among patients investigated with complementary exams. Denominators are used when the number of patients is different from the whole sample indicated at the top of the column.

Initial Model			Final Model	
Variables	OR (95% CI)	p-value	OR (95% CI)	p-value
Country (Spain)	0.59 (0.398-0.880)	0.010	0.51 (0.359-0.726)	<0.001
Age	1.02 (1.010-1.035)	<0.001	1.02 (1.008-1.032)	0.001
Neutropenia	2.99 (1.437-6.258)	0.003	3.24 (1.594-6.585)	0.001
Chronic pulmonary disease	2.13 (1.400-3.265)	<0.001	2.26 (1.495-3.436)	<0.001
Liver disease	1.47 (0.881-2.475)	0.140	-	-
Renal insufficiency	1.34 (0.932-1.936)	0.114	-	-
Corticosteroids	1.37 (0.945-1.989)	0.096	1.45 (1.018-2.079)	0.039
Antibiotics	1.48 (0.891-2.479)	0.129	-	-
Previous surgery	0.72 (0.502-1.053)	0.091	-	-
Pitt Score >1	2.63 (1.804-3.843)	<0.001	2.56 (1.776-3.690)	<0.001
Candida parapsilosis	0.39 (0.244-0.626)	<0.001	0.36 (0.233-0.568)	<0.001
Candida tropicalis	1.18 (0.730-1.933)	0.487	-	-
Candida glabrata	1.97 (0.984-3.974)	0.056	-	-
Country x Candida glabrata**	0.32 (0.119-0.867)	0.025	-	-
Inadequate therapeutic management***	2.81 (1.657-4.794)	<0.001	2.84 (1.685-4.800)	<0.001

***Table 6*: Multivariate logistic regression model for independent factors associated with 30-day mortality in 720 candidemic adults diagnosed at public tertiary hospitals in Brazil and Spain from 2010 to 2018**
OR: odds ratio; CI: confidence interval; *Final model after excluding non-significant variables one by one by order of significance (backwards stepwise method);** Interaction between country and *C. glabrata*;*** Patients without effective antifungal and CVC removal within 48 h.

4·800), $p < 0·001$]. Protective factors included candidemia due to *C. parapsilosis* [OR 0·36, 95%CI (0·233-0·568), $p < 0·001$], and being from Spain [OR 0·51, 95%CI (0·359-0·726), $p < 0·001$].

4. Discussion

We analysed a large series of candidemic adults diagnosed at five tertiary public hospitals from countries with different socioeconomic backgrounds and very distinct historical trends in mortality rates associated with candidemia over nine years. When compared to Spain, our data shows a persistently higher mortality rate among Brazilian patients as well as contrasting epidemiology and therapeutic practices, which have impacted both early (35·8% vs. 20·1%, $p < 0·001$) and late mortality (51·9% vs. 31·6%, $p < 0·001$), even among cases with less severe clinical presentation. In agreement with our findings, other studies with no direct comparison have also found similar mortality rates in

Brazil [2,10] and Spain [3,7]. Moreover, the independent predictors of 30-day mortality among adult patients with candidemia observed in our study included mainly underlying conditions related with the host, and therapeutic practices, as previously reported [2,3,5,14–16].

Epidemiology and host characteristics are known to be strongly associated with the prognosis of candidemia [17–19]. In the Spanish cohort, although candidemia affected slightly older patients with a personal history of active cancer, they often presented a surgical profile (36·2% vs. 26·4%, $p = 0.006$), which has been associated with a better prognosis when compared to clinical patients admitted to non-surgical wards [5,20]. In contrast, Brazilian patients had a higher proportion of diagnosis at intensive care units (46·9% vs. 21·1%, $p < 0.001$), with all the characteristics that would be expected in such scenario, including a more severe clinical presentation, higher incidence of renal insufficiency and use of steroids, all known factors associated with a worse prognosis [2,3,5,19]. These results suggest that candidemia awareness in non-ICU settings may need to be enhanced in Brazilian centres, triggering prompt diagnosis and management before clinical deterioration sets in and intensive care is needed. This finding is in consonance with the higher number of Brazilian patients who were not treated with antifungal drugs, probably due to a delay of clinicians in getting culture results and early death. Thus, faster diagnostic tools and active antifungal stewardship programs are warranted [21,22].

Candida species may play an important role when it comes to virulence mechanisms and how they may impact patient prognosis [23,24]. Interestingly, *C. tropicalis* was more likely to be isolated from Brazilian patients (17·6% vs. 9·3%, $p = 0.002$) and, although our data do not support it as an independent factor associated with mortality, this species has been previously associated with more severe and lethal cases of invasive candidiasis [24,25]. On the contrary, candidemia due to *C. parapsilosis* has been linked to lower mortality rates [26], which was suggested in our results for its protective effect in the multivariant logistic regression. In addition, the proportion of *C. glabrata* in Brazil was similar to Spain, confirming that its incidence has been growing continuously, probably due to population characteristics and practices regarding antifungal use [9,18,27].

Therapeutic management including the combination of prompt effective antifungal and source control are essential for better clinical outcomes [5,28,29]. In our series, inadequate therapeutic management was an independent factor associated with 30-day mortality that remained significant even after adjusting for between-country differences. Also, antifungals were started earlier in the Spanish cohort, confirming the impact of timing on patient prognosis in agreement with other authors [5,16,29,30]. Fluconazole was still the initial antifungal most commonly prescribed in both cohorts, what would probably be more suitable to Spanish patients, since they were less likely to be critically ill [13]. Nevertheless, these patients also received an echinocandin more often at some point during the candidemia episode, especially those in the ICU (73·0% vs. 39·5%, $p < 0.001$). These results align with other studies that report better clinical outcomes with echinocandins [2,5,25].

The clinical benefits of CVC removal are mainly expected when the CVC is the source of infection [16]. Unfortunately, due to the retrospective nature of this study, no consistent information as an attempt to confirm CVC-related candidemia could be retrieved for all patients. Another recurrent controversial topic consists on the clinical impact of the timing of CVC removal during the episode of candidemia [31]. Our results show that Brazilian centres had a higher proportion of CVC removal at any time during the episode of candidemia, but Spanish patients underwent early CVC-removal more often, favouring a lower mortality rate as previously published [16,30]. Such difference could be interpreted as a marker of clinical severity since patients presenting with less severe cases are more likely to be selected for early CVC removal. Nevertheless, the mortality rate in Brazil was significantly higher even among less severe cases (Pitt-Score ≤1), suggesting that there might be room for management improvement.

Lately, several studies proposing a bundle of care to systematize candidemia treatment and improve patient quality of care have been published, often including screening for complications such as chorioretinitis and endocarditis [32–35]. However, there is still no consensus on which patients would benefit most from undergoing such complementary tests [33]. As an example, although the incidence of chorioretinitis among patients with candidemia is relatively high, there is usually no significant impact on prognosis or switch on management strategy to support the indication of routinely performing ophthalmoscopy [36]. Even though this may be changing overtime, our results show that ophthalmoscopy and echocardiograms were more frequently performed among Spanish patients, in alignment with international guidelines [13,37]. Furthermore, while current European guidelines support routine echocardiogram for every candidemic patient, Brazilian guidelines recommend it mainly to those with persistent candidemia or clinical deterioration with signs and symptoms of endocarditis [38]. In our study, the overall proportion of diagnosed endocarditis from Brazilian vs. Spanish patients was similar (1·8% vs. 2·2%, $p = 0.789$). Yet, the percentage of endocarditis among the Brazilian patients who underwent an echocardiogram was higher, suggesting a better test efficiency when clinical suspicion, persistent candidemia, haemodialysis, previous valve disease, presence of cardiovascular prothesis, or other risk factors are required to indicate the exam.

Our study has some limitations, including its retrospective nature, which might have restricted the detailing of data collection, potentially precluding relevant analyses. Although data was only used when the dictionary of terms from both countries was compatible, some important information that could have helped to understand prognostic variability, such as the level of severity of patients' comorbidities, or the most likely primary source of candidemia, could not be consistently retrieved due to differences in definitions. Also, information on other forms of infection source control besides CVC-removal were not collected in all centres. Thus, this study could be underpowered to thoroughly account for further between-country differences, and therefore, conclusions should be made with caution. Nevertheless, studies proposing a direct comparison regarding the epidemiology, therapeutic management and outcomes of candidemia in public tertiary hospitals from countries with different social and economic backgrounds are scarce and bring practical insights for improvement.

5. Conclusions

Higher mortality rates were observed in Brazil among adults with candidemia when compared to Spain. These findings were mainly associated with characteristics related to the host and inadequate therapeutic management. Thus, although epidemiological differences may contribute towards a disparity of mortality rates between countries, well-known modifiable therapeutic strategies, such as both effective and prompt initiation of antifungals combined with CVC-removal still need to be emphasized in order to improve the prognosis of adults with candidemia.

Contributors

Caroline Agnelli: Visualization, study design, data curation, Formal analysis, writing original draft, writing review and editing.

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Declaration of Competing Interest

ALC has received educational grants from Amgen, Biotoscana-Knight, Pfizer, Gilead Sciences, and United Medical. FQT has received consulting fees for Pfizer, TEVA and United Medical. TG has received educational grants from Merck Sharp & Dohme (MSD). TS has received support for attending meetings from Pfizer and MSD. PM has received educational grants from Angelini, Astellas, Basilea, Gilead Sciences, MSD, Nabriva, Novartis, Pfizer, Roche, and Werfen. MV has received educational grants from Pfizer, GSK, MSD, and Angellini. JG has received educational grants from Astellas, Gilead, Pfizer, MSD, and United Medical. The remaining authors declare no conflicts of interest.

Data sharing statement

Anonymized data may be available upon well-detailed and pertinent request. Please contact the corresponding authors.

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