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**Title: Evaluation of first-line therapies for the treatment of candidemia in ICU patients:  
a propensity score analysis**

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## Summary

### Background

Candidemia is a major cause of mortality in the intensive care unit (ICU). According to the Infectious Diseases Society of America (IDSA), an echinocandin is recommended as initial therapy and fluconazole, as an alternative. In a context of echinocandin resistance development, the question arising is whether azoles are a suitable alternative to echinocandins for the treatment of candidemia in critically ill patients.

### Methods

A 3-year (2015-2017) retrospective multicentric cohort study was conducted. Adult patients with a diagnosis of candidemia during the ICU stay and treated with echinocandins or azoles were included. Demographic, clinical data, mycological data, and antifungal treatments, were collected. Kaplan-Meier survival analysis, univariate analysis, and a multivariate logistic regression analysis using a propensity score with the inverse probability of treatment weighting method, were performed.

### Findings

Seventy-nine patients (n=79) were analyzed. Treatment success, as well as survival on day 90 (Kaplan-Meier survival analysis, log rank test,  $p=0.542$ ), were comparable between patients who received echinocandins (caspofungin (n=47)) or azoles (fluconazole (n=29) or voriconazole (n=3)). A multivariable analysis demonstrated that higher SOFA score on the day of candidemia diagnosis and absence of adequate *Candida* source control were independently associated with a greater risk of 90-day mortality, whereas azoles treatment was not associated with an excess 90-day mortality.

### Interpretation

This study confirms that the use of azoles recommended for candidemia, mostly fluconazole, as a first-line therapy is a reasonable alternative to caspofungin for ICU patients in our institution. This needs to be included in local guidelines through antifungal stewardship programs.

**Keywords:** candidemia; caspofungin; fluconazole; voriconazole; mortality; propensity score

## Introduction

Invasive fungal infections are responsible for over 1.6 million deaths each year (1). In intensive care units (ICU), invasive candidiasis predominates with an estimated incidence of 2.1 to 6.7 per 1000 admissions (2). Candidemia known as the most common manifestations of invasive candidiasis has an attributable mortality up to 40% and is then recognized as a major cause of mortality in the ICU (3, 4).

According to the Clinical Practice Guideline for the Management of Candidiasis by the Infectious Diseases Society of America (IDSA)(5), an echinocandin (caspofungin, micafungin, or anidulafungin) is recommended as initial therapy. Fluconazole is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species (5). Voriconazole is effective for candidemia and offers little advantage over fluconazole as initial therapy for patients who have fluconazole-resistant isolates of *C. krusei*, *C. guilliermondii* or *C. glabrata* that are voriconazole-susceptible (5). Interestingly, despite favorable characteristics of echinocandins compared to azoles including fungicidal activity, broad spectrum, safety profile, and few drug interactions (6), azoles are still widely used in ICU as demonstrated by a prospective observational cohort study that showed echinocandin accounting for 63.4% of the prescriptions and azoles for 34.5% in ICU (7). Then, the use of echinocandins versus azoles in ICU patients is still a matter of debate. This is particularly true in a context of emergence of *C. auris* and *Candida* resistance to echinocandins (8). Importantly, echinocandins resistance in *C. glabrata* can be associated with cross-resistance to azoles thus leading to multi-drug resistant strains (8). This raises the question of the large use of echinocandins to avoid the development of resistant strains. Moreover, the demonstration that most of *Candida* isolates recovered in the ICU were susceptible to fluconazole gives the opportunity to use azoles for candidemia treatment of patients admitted in the ICU (4, 6).

In this context, the question arising is whether azoles, including fluconazole and voriconazole, are a suitable alternative to echinocandins for the treatment of candidemia in critically ill patients with the aim of implementing local guidelines as recently suggested (9). We thus conducted a retrospective multicenter cohort study in Lyon University Hospital to investigate the local epidemiology of *Candida* and antifungal treatments used in patients suffering from candidemia in ICU. This study was part of an antifungal stewardship program implemented in our institution which major aim is to contain resistance through the optimal use of antifungals on an individual patient basis (10).

## Materials and methods

### Study design

This study was a 3-year (2015-2017) retrospective multicenter cohort study using Hospital database. Six ICUs including medical (two units), surgical (one unit), and medical surgical (three units) ICUs, were involved and located in four medical centers. Adult patients > 19 years-old with a diagnosis of candidemia during the ICU stay and treated with echinocandins or azoles were included in the study. Candidemia was defined as at least one blood culture positive for *Candida*. The date of candidemia was the day of the first blood culture positive for *Candida*. There was no age limit for inclusion. Neutropenic patients, patients who did not receive antifungals, patients with a fungal co-infection, patients who received antifungal therapy within 7 days before candidemia diagnosis, and patients who received liposomal amphotericin b or multiple antifungal agents as first-line therapy, were not included. Patients were categorized into two groups: patients receiving first-line therapy with echinocandins, i.e., caspofungin, and patients receiving azoles, i.e. fluconazole or voriconazole. First-line therapy was defined as the first antifungal agent administered at the onset of candidemia **regardless of treatment duration**. During the study period,

major diagnostic, therapeutic, and infection control standards, remained unchanged. The study was registered in Clinicaltrials.gov (NCT03799172).

### **Ethical approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional research committee and with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the institutional Ethics Committee (N°19-37). Due to the retrospective nature of the study, formal consent was not required. Electronic records were under the auspice of the French National Committee for Data Protection and Freedom of Information.

### **Data collection**

The following data were collected: age, gender, main underlying disease, previous abdominal surgery within 30 days before candidemia, dates of ICU admission and discharge, dates of hospital admission and discharge, SAPSII score on ICU admission, SOFA score on the day of candidemia, septic shock (clinically identified by a vasopressor requirement) on the day of candidemia, prescription of an antifungal within 30 days before candidemia diagnosis, antifungal regimen (molecule, dose, duration), occurrence of complications (endocarditis, thrombophlebitis, endophthalmitis), adequate source control of *Candida* including removal of central venous catheter or surgical procedures to drain abscesses, mycological results (date of positive blood culture, *Candida* species, susceptibility profile, and if applicable, date of negative blood culture), and all cause hospital mortality at the end of antifungal treatment, on day 30, and on day 90. To ensure reproducibility and completeness of data extraction, an Excel spread sheet (Microsoft Corp., Redmond, WA, USA) compiling all variables to be extracted was used. Clinicians were in charge of clinical data collection and pharmacists, of biological data, as well as collection of antifungal regimen. Data extraction was double-checked by ALB. Disagreements over data extraction were



resolved by discussion. Provided data were centrally checked by an independent operator for completeness, plausibility, and integrity before synthesis.

### **Evaluation of outcome**

The primary outcome variable was all cause hospital mortality on day 90. The secondary outcome was treatment success on day 30. Treatment success was assessed according to Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria (11). Treatment success was defined as a complete response if the following two criteria were full-filled: survival and resolution of all attributable symptoms and signs of disease, and mycological success (documented clearance of pathogen from the blood). Treatment success was defined as a partial response if the following two criteria were full-filled: survival and improvement of attributable symptoms and signs of disease, and documented clearance of blood. In case of persistent or recurrent fever despite clearance of blood, this situation should equate with a complete response (11)(12). Treatment failure included stable response, progression of disease, and death. Stable response was defined as survival and minor or no improvement in attributable symptoms and signs of disease, and persistent isolation of *Candida* species from blood. Progression of disease was defined as persistent isolation of *Candida* species from blood associated with worsening of clinical symptoms or signs of disease (e.g., septic shock, progression of hematogenous cutaneous candidiasis).

### **Statistical analysis**

Categorical variables were analyzed with Chi-square test or with Fisher's exact test, as appropriate. Continuous variables were analyzed by Mann-Whitney U test. A univariable analysis of groups, followed by a univariable analysis for 90-day mortality including potentially relevant variables for our purpose, was performed. To face the lack of randomisation, a propensity score was calculated for each patient including the most significant ( $p < 0.2$ ) and/or relevant variables between

echinocandin and azoles groups (i.e. age, diabetes mellitus, cirrhosis, solid organ transplantation (SOT), solid cancer, hematological cancer, chronic heart failure, abdominal surgery within 30 days of candidemia, LOS in ICU before candidemia, SAPSII, SOFA, septic shock and mechanical ventilation). Model discrimination was analyzed by evaluating the area under the Receiver Operating Characteristic (ROC) curve: the logistic regression model used for the propensity score calculation gave an area under the ROC curve of 0.848 (95% CI 0.766-0.931).

A multivariable logistic regression analysis of 90-day mortality was performed to adjust for differences in the most relevant and significant variables ( $p < 0.05$ ) between alive and deceased patients at day 90 (i.e., SOT, SOFA on the day of candidemia, time elapsed to treatment initiation, adequate *Candida* source control, first-line antifungal). Factors contributing to multicollinearity (i.e. SAPSII, septic shock) were excluded from the multivariable analysis. The multivariable model was weighted using the Inverse Probability of Treatment Weighing (IPTW) method based on the propensity score. Adjusted odd ratios were calculated with their respective 95% CIs. Kaplan-Meier survival analyses were performed to show the relationship between therapeutic strategies and 90-day mortality; the differences in survival were assessed using the log-rank test (Mantel-Cox). R 3.5.2 software (R Foundation for Statistical Computing, Vienna, Austria) was used for propensity score and multivariable analyses, and SPSS V21.0 software (IBM SPSS, Chicago, USA), for Kaplan-Meier survival analyses. P-value  $< 0.05$  was considered statistically significant.

## **Results**

### **Baseline characteristics**

A total of 104 patients had a candidemia during their ICU stay from 2015 to 2017 (Figure 1) corresponding to a candidemia incidence of 3.5/1000 and 4.6/1000 admissions, in medical and surgical ICU respectively. Of these, 79 patients were included in the study. Forty-seven ( $n=47$ )

patients received an echinocandin (caspofungin) and 32 received azoles (fluconazole n=29 and voriconazole n=3) as first-line therapies. Twenty-five patients were not included: 13 patients did not receive any antifungal treatment, six patients were treated with antifungals before candidemia, five patients received another antifungal than azoles or echinocandin, and one patient had a co-infection with *Aspergillus*. Baseline characteristics were comparable for both echinocandin and azoles-treated patients, except for previous abdominal surgery that were more prevalent in echinocandin group and length of stay (LOS) in ICU before candidemia that was longer in echinocandin group compared to azoles group (Table 1).

### **Mycological findings**

The distribution of *Candida* species and the proportion of *Candida* with decreased susceptibility were similar in the two groups (Table 1). The most common species causing candidemia were *C. albicans* and *C. glabrata* accounting respectively for 40.5% (32/79) and 26.6% (21/79) (Table 1). Multiple *Candida* isolates were recovered for 8.5% (4/47) patients in echinocandin group, including a co-infection of *C. albicans*/*C. kefyr*, *C. albicans*/*C. glabrata*, *C. krusei*/*C. kefyr*, and *C. dubliniensis*/*C. glabrata* (Table 1). The median times to negative blood culture for overall *Candida*, as well as *C. albicans*, were similar for echinocandin and azoles groups (p=0.878 and p=0.546, respectively for overall *Candida* and *C. albicans*) (Table 1).

### **Antifungal treatment and length of stay**

All first-line therapies were considered adequate according to *Candida* antifungal susceptibility profile. Durations of first-line and overall antifungal treatment were comparable between echinocandin and azoles groups, as well as time elapsed to treatment initiation and adequate control of *Candida* source including removal of central venous catheter and surgical procedures to drain abscesses (Table 1). As expected, duration of antifungal treatment was longer in alive patients compared to deceased patients (Table 2). LOS in ICU before the onset of candidemia was longer for

patients treated with echinocandin compared to azoles, as demonstrated by medians of 8 and 1.5 days respectively ( $p=0.030$ ) (Table 1). LOS in ICU after the onset of candidemia was prolonged for patients who were treated with echinocandin, but were deceased on day 90, compared to azoles ( $25.0 \pm 26.5$  days and  $13.3 \pm 12.3$  days ( $p=0.045$ ), respectively for caspofungin and azoles groups) (Table 1).

### **Treatment success and mortality**

Complete response on day 30, as well as mycological success on day 30, were comparable between echinocandin and azoles groups (Table 1). In the overall population, the mortality rates at the end of antifungal treatment, on day 30, and on day 90, were respectively 43.0% (34/79), 49.4% (39/79), and 53.3% (42/79). The all cause hospital mortality rates were similar in echinocandin and azoles-treated patients at the end of antifungal treatment ( $p=0.135$ ), on day 30 ( $p=0.581$ ), and on day 90 ( $p=0.650$ ) (Table 1). These results were confirmed by Kaplan-Meier survival analysis that demonstrated that survival on day 90 was comparable between patients who received echinocandin (caspofungin) and those who received azoles (fluconazole or voriconazole) (log rank test,  $p=0.542$ , Figure 2). Candidemia with a median time to death of 13 days is rapidly fatal despite antifungal treatment initiation in a median time of 2 days in the overall population. It has to be noticed that mean time elapsed to antifungal initiation in deceased patients was shorter compared to alive patients, respectively  $1.7 \pm 1.5$  and  $2.7 \pm 2.1$  days ( $p=0.016$ ) (Table 2). Moreover, higher SAPSII or higher SOFA score was demonstrated in deceased compared to alive patients ( $p=0.010$  and  $p<0.001$ , respectively) and all patients who were deceased on day 90 presented with a septic shock on the day of candidemia compared to 75.7% for alive patients ( $p<0.001$ ) (Table 2).

A multivariable logistic regression analysis based on propensity score with IPTW revealed that azoles treatment was not associated with a greater risk of all cause hospital 90-day mortality ( $p=0.196$ ) (Table 3). Multivariable analysis also demonstrated that higher SOFA score on the day of

candidemia, a shorter time to antifungal initiation, and absence of adequate *Candida* source control were independently associated with a greater risk of 90-day mortality in the overall population ( $p < 0.001$ ) (Table 3). Whereas SOT was more prevalent in alive compared to deceased patients on day 90 ( $p = 0.023$ ) (Table 2), multivariable logistic regression failed to demonstrate that SOT was associated with a reduction in 90-day mortality ( $p = 0.147$ , Table 3).

## Discussion

In a context of echinocandins resistance development, we studied the local epidemiology of *Candida* and addressed the issue of azoles use (mostly fluconazole) in ICU patients suffering candidemia through a retrospective multicenter study using a propensity score analysis. Fluconazole is indeed an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species according to IDSA guidelines (5). This recommendation is based on a study that showed anidulafungin to be non-inferior to fluconazole in the treatment of invasive candidiasis: anidulafungin was successful in 75.6% of patients, as compared with 60.2% for fluconazole (12). Candidemia is a common disease in ICU patients as demonstrated by the estimated incidence of 3.5/1000 and 4.6/1000 admissions, respectively in medical and surgical ICU. The main underlying diseases in this cohort of ICU patients suffering candidemia included diabetes, solid cancer, chronic kidney disease, and chronic heart disease. Baseline characteristics of patients treated with echinocandin and azoles were comparable, except for LOS in ICU before candidemia and previous abdominal surgery. The median LOS of 8 days in ICU before candidemia onset was indeed longer in echinocandin group compared to a median of 1.5 days in azoles group; this may account for the longer ICU LOS of patients treated with echinocandin compared to azoles. The longer LOS of patients in echinocandin group may be explained by a higher proportion of patients who underwent abdominal surgery compared to azoles group. Twenty-two ( $n = 22$ ) patients had previous abdominal surgery with most of them ( $n = 18$ ) receiving caspofungin; the more frequent use

of echinocandin for patients with previous abdominal surgery was in agreement with IDSA guidelines that recommend an echinocandin as initial therapy for patients who had recent abdominal surgery (5). Of note, previous abdominal surgery was not associated with a poorer outcome on day 90.

Despite an antifungal treatment initiated with a median time of 2 days, candidemia was still a highly fatal disease in ICU associated with a mortality rate of 43.0% on day 30 and 53.3% on day 90, which is consistent with a recent European study on invasive candidiasis in ICU that reported a 30-day mortality of 42% (13). Short first-line antifungal treatments were not an exclusion criteria as this may exclude the most critically ill patients more prone to early deceased and consequently, to receive short treatments. The shorter mean time elapsed to antifungal initiation shown in deceased compared to alive patients may be in relation with the critical illness of deceased patients who demonstrated to have higher SOFA score and SAPSII compared to alive patients. In this cohort of patients suffering candidemia during their ICU stay, Kaplan-Meier survival analysis and a multivariable logistic regression model based on propensity score with IPTW revealed that azoles treatment, mostly fluconazole, was not associated with a greater risk of 90-day mortality in ICU patients compared to caspofungin. Of note, factors that may impact 90-day mortality such as SAPSII, SOFA score, septic shock, durations of antifungal treatments, time elapsed to treatment initiation, and adequate control of *Candida* source, were comparable between echinocandin and azoles groups. This result is in line with an observational study that demonstrated no significant association between initial antifungal treatment with echinocandins and 28-day mortality (14). But, this is not the case of another study that showed the use of echinocandins for candidemia to be a protective factor (15): 58 patients deceased on day 90 in fluconazole group compared to 51 in echinocandin group. The protective advantage of echinocandins may be explained by the high number of patients (n=10) in fluconazole group that received inappropriate antifungal therapy

whereas all patients received appropriate therapy in echinocandin group. In our series, all azoles treatments were considered appropriate.

In respect with previous studies (7, 16–18), multivariable analysis identified higher SOFA score and absence of adequate *Candida* source control to be independent predictors of mortality. The need for an early adequate source control in critically ill patients with invasive candidiasis was recently recalled by the ESICM/ESCMID task force (19). Whereas SOT was more prevalent in alive compared to deceased patients, multivariable analysis failed to demonstrate a decrease in 90-day mortality for SOT patients; this may be in relation with the low number of patients who received SOT (n=8). Anidulafungin was previously demonstrated to be associated with significantly faster clearance of blood cultures compared to fluconazole for patients with *C. albicans* infections (16); this was not the case in our series in which no difference was observed in median time to negative blood culture between echinocandin and azoles groups for overall *Candida*, as well as for *C. albicans*.

This study has some limitations. This is a retrospective study that did not allow a randomization of patients, but this was overcome by the use of a propensity score with the aim to reach the conditions of a randomized controlled trial. The area under the ROC curve was 0.848, indicating the good ability of the score to accurately predict group assignment. Monitoring of caspofungin and azoles levels were not available for all patients, thus rendering drug exposure of patients non evaluable. Caspofungin was the only echinocandin used in this multicenter study, but most experts agree that these agents are sufficiently similar to be considered interchangeable (20, 21).

This study suggests that the use of recommended azoles for candidemia, mostly fluconazole, is a reasonable alternative to caspofungin for ICU patients suffering candidemia in regards to the local epidemiology of *Candida*. In a context of increasing *Candida* resistance, this study highlights the

need to evaluate the clinical practice; it supports indeed the implementation of local guidelines through antifungal stewardship programs that promote the optimal use of antifungals.



**Authors' contributions**

A.L.B., C.G., F.A., J.L.F., A.F., J.M., C.M., T.R., V.P., C.C., L.A., and G.L., designed the study. A.L.B., A.F., C.G., R.H., C.M., S.P., and G.L., contributed to data extraction. A.L.B., P.P., C.G., L.A., and G.L., analysed the data. All authors contributed to the interpretation of results and revised the different versions of the manuscript.

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None

**Conflict of interest**

None

**Ethical approval**

Ethical approval was obtained from the Ethics Committee (N°19-37) of Hospices Civils de Lyon, France.

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**Figure legends**

**Figure 1:** Clinical flow chart

**Figure 2:** Kaplan-Meier analysis of survival to 90 days among patients with candidemia (log-rank test,  $p=0.542$ )

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**Table 1: Baseline characteristics and outcomes according to antifungal treatment**

Characteristics	Echinocandins (n=47)	Azoles (n=32)	<i>p</i>
<b>Clinical features</b>			
Age (years)	62.3 ± 10.9	63.0 ± 15.3	0.473
Male sex, n (%)	36 (76.6)	24 (75.0)	0.870
Medical ICU	15 (31.9)	14 (43.8)	0.284
Diabetes mellitus, n (%)	18 (38.3)	6 (18.8)	0.064
Cirrhosis, n (%)	7 (14.9)	3 (9.4)	0.731
Necrotizing pancreatitis, n (%)	3 (6.4)	1 (3.1)	0.643
Chronic heart failure, n (%)	6 (12.8)	9 (28.1)	0.087
Chronic kidney disease, n (%)	10 (21.3)	6 (18.8)	0.783
Solid cancer, n (%)	8 (17.0)	10 (31.3)	0.139
Solid organ transplantation, n (%)	5 (10.6)	3 (9.4)	1
Hematological cancer, n (%)	8 (17.0)	2 (6.3)	0.188
Glucocorticoids > 1 mg/kg/d, n (%)	9 (19.1)	7 (21.9)	0.767
SAPSII on ICU admission	58.0 ± 18.0	55.0 ± 20.9	0.379
SOFA score on the day of candidemia	8.1 ± 4.5	7.9 ± 5.3	0.830
Septic shock on the day of candidemia, n (%)	42 (89.4)	28 (87.5)	0.798
<b>Clinical course</b>			
Previous abdominal surgery, n (%)	18 (38.3)	4 (12.5)	0.012
Previous antifungal, n (%)	10 (21.3)	2 (6.3)	0.067
LOS in ICU before candidemia (days)	8 [0-102]	1.5 [0-66]	0.030
LOS in ICU (days)			
All patients	25.0 [1-152]	11.0 [2-92]	0.012
Alive	38.0 [4-152]	14.5 [5-92]	0.239
Dead	24.0 [1-142]	11.0 [2-45]	0.045
LOS in Hospital (days)			
All patients	35.0 [1-224]	26.0 [2-144]	0.192
Alive	61.0 [13-224]	81.0 [15-144]	0.575
Dead	25.0 [1-142]	12.5 [2-45]	0.067
<b>Mycological results</b>			
<i>C. albicans</i> , n (%)	17 (36.2)	15 (46.9)	0.447
<i>C. glabrata</i> , n (%)	13 (27.6)	8 (25.0)	0.793
<i>C. tropicalis</i> , n (%)	7 (14.9)	5 (15.7)	1
<i>C. parapsilosis</i> , n (%)	2 (4.3)	2 (6.2)	1
<i>C. krusei</i> , n (%)	3 (6.4)	1 (3.1)	0.643
<i>C. kefyr</i> , n (%)	1 (2.1)	1 (3.1)	1
Multiple <i>Candida</i>	4 (8.5)	0 (0.0)	0.142
<b><i>Candida</i> with decreased susceptibility, n (%)</b>	16 (34.0)	9 (28.1)	0.892
Time to negative blood culture (days)	4.0 [1-32]	3.0 [1-25]	0.878
<b>Treatment</b>			
Time elapsed to treatment initiation (days)	2 [0-10]	2 [0-6]	0.499
Duration of first-line antifungal (days)	7.0 [1-190]	5.5 [2-37]	0.441
Total duration of antifungals (days)	14.5 [2-541]	11.0 [2-47]	0.336
Patients who switched to oral, n (%)	3 (6.4)	3 (9.4)	0.622
Adequate <i>Candida</i> source control, n (%)	39 (83)	21 (65.6)	0.076
<b>Outcomes</b>			
30-day mycological success, n (%)	43 (91.5)	26 (81.3)	0.179
30-day complete response, n (%)	25 (53.2)	13 (40.6)	0.272
Mortality at the end of antifungal treatment, n (%)	17 (36.2)	17 (53.1)	0.135
30-day mortality, n (%)	22 (46.8)	17 (53.1)	0.581
90-day mortality, n (%)	24 (51.1)	18 (56.3)	0.650
Time to death (days)	12.0 [1-148]	15.0 [3-201]	0.698
Complications, n (%)	4 (8.5)	6 (18.8)	0.307

Data are number (%), mean ± standard deviation, or median [range], as appropriate. ICU: intensive care unit; LOS: length of stay; SAPSII: simplified acute physiologic score; SOFA: sepsis-related organ failure assessment

**Table 2: Univariable analysis of factors associated with 90-day mortality**

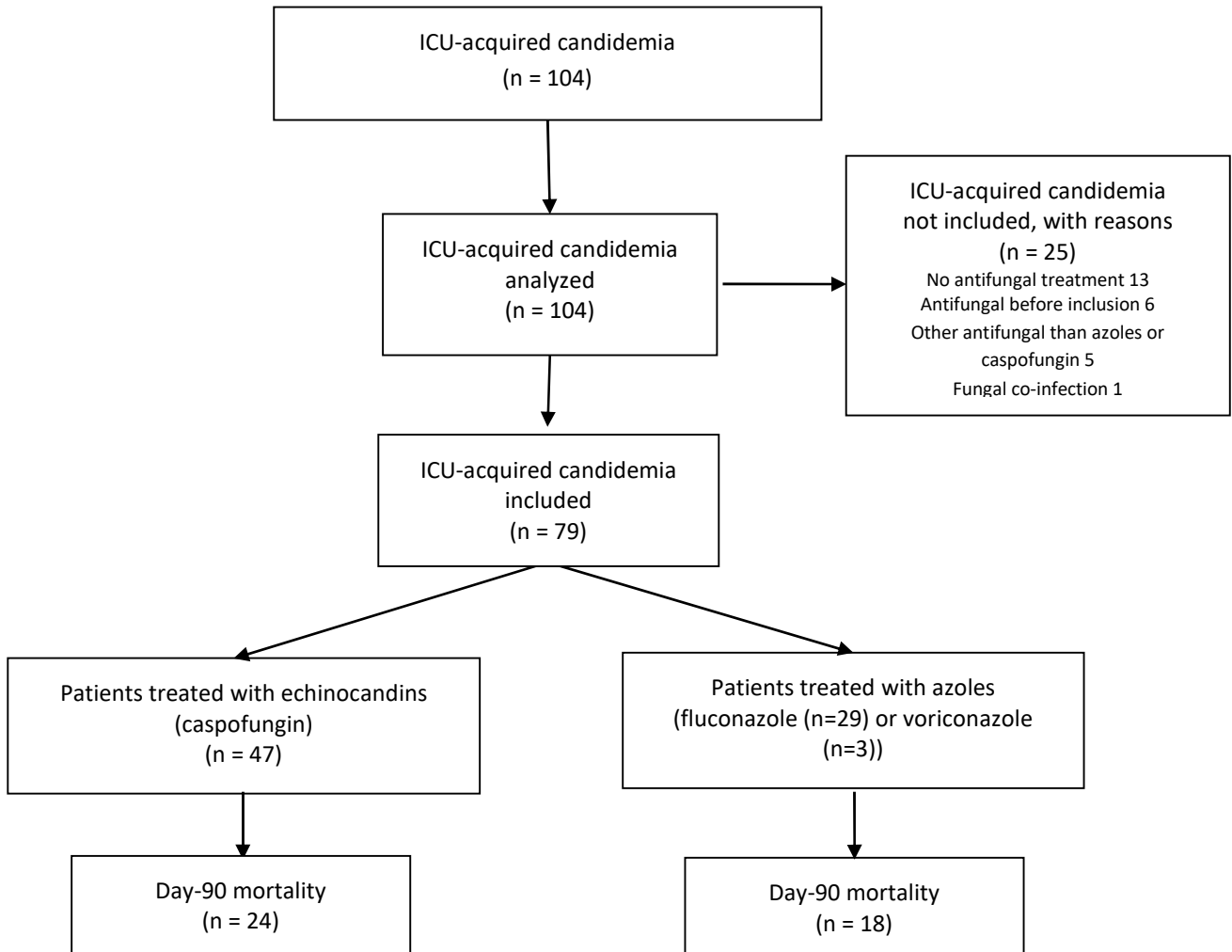
Characteristics	Dead (n=42)	Alive (n=37)	<i>p</i>
<b>Clinical features</b>			
Age (years)	62.8 ± 14.7	59.6 ± 13.2	0.067
Male sex, n (%)	33 (78.6)	27 (73.0)	0.561
Medical ICU	17 (40.5)	12 (32.4)	0.744
Diabetes mellitus, n (%)	13 (31.0)	11 (29.7)	0.906
Cirrhosis, n (%)	8 (19.0)	2 (5.4)	0.094
Necrotizing pancreatitis, n (%)	1 (2.4)	3 (8.1)	0.336
Chronic heart failure, n (%)	9 (21.4)	6 (16.2)	0.556
Chronic kidney disease, n (%)	7 (16.7)	9 (24.3)	0.398
Solid cancer, n (%)	11 (26.2)	7 (18.9)	0.442
Solid organ transplantation, n (%)	1 (2.4)	7 (18.9)	0.023
Hematological cancer, n (%)	6 (14.3)	4 (10.8)	0.643
Glucocorticoids > 1 mg/kg/d, n (%)	8 (19.0)	8 (21.6)	0.776
SAPSII on ICU admission	58.4 ± 21.8	51.0 ± 17.9	0.010
SOFA score on the day of candidemia	9.9 ± 5.5	6.2 ± 4.9	< 0.001
Septic shock on the day of candidemia, n (%)	42 (100.0)	28 (75.7)	< 0.001
<b>Clinical course</b>			
Previous abdominal surgery, n (%)	10 (23.8)	12 (32.4)	0.394
Previous antifungal, n (%)	7 (16.7)	5 (13.5)	0.697
LOS in ICU before candidemia (days)	7 [1-142]	5 [4-152]	0.044
<b>Mycological results</b>			
<i>C. albicans</i> , n (%)	18 (42.9)	14 (37.8)	0.650
<i>C. glabrata</i> , n (%)	11 (26.2)	10 (27.0)	0.933
<i>C. tropicalis</i> , n (%)	7 (16.7)	5 (13.5)	0.697
<i>C. parapsilosis</i> , n (%)	0 (0.0)	4 (10.8)	0.044
<i>C. krusei</i> , n (%)	2 (4.8)	2 (5.4)	0.877
<i>C. kefyr</i> , n (%)	1 (2.4)	1 (2.7)	1
Multiple <i>Candida</i>	3 (7.1)	1 (2.7)	0.618
<b><i>Candida</i> with decreased susceptibility, n (%)</b>	13 (31.0)	12 (32.4)	0.887
Time to negative blood culture (days)	3 [1-18]	4 [1-32]	0.271
<b>Treatment</b>			
Time elapsed to treatment initiation (days)	2 [0-6]	2 [0-10]	0.016
Antifungal			0.650
Caspofungin	24 (57.1)	23 (62.2)	
Azoles	18 (42.9)	14 (37.8)	
Duration of first-line antifungal (days)	4 [1-190]	13 [3-119]	< 0.001
Total duration of antifungals (days)	10 [2-190]	16 [3-541]	0.003
Patients who switched to oral, n (%)	1 (2.4)	5 (13.5)	0.093
Adequate <i>Candida</i> source control, n (%)	27 (64.3)	33 (89.2)	0.010

Data are number (%), mean ± standard deviation, or median [range], as appropriate. ICU: intensive care unit; LOS: length of stay; RRT: renal replacement therapy; SAPSII: simplified acute physiologic score; SOFA: sepsis-related organ failure assessment

**Table 3: Multivariable analysis of risk factors for 90-day mortality**

<b>Risk factor</b>	<b>Adjusted odds ratio</b>	<b>95% CI</b>	<b>P</b>
<b>Solid organ transplantation</b>	0.251	0.037-1.624	0.147
<b>SOFA on the day of candidemia</b>	1.363	1.214-1.530	<0.001
<b>Time elapsed to treatment initiation</b>	0.564	0.406-0.783	<0.001
<b>Adequate <i>Candida</i> source control</b>	0.048	0.011-0.211	<0.001
<b>Azoles first-line therapy</b>	1.898	0.719-5.006	0.196

CI: confidence interval; ICU: intensive care unit; SOFA: sepsis-related organ failure assessment

**Figure 1:** Clinical flow chart

**Figure 2:** Kaplan-Meier analysis of survival to 90 days among patients with candidemia (log-rank test,  $p=0.542$ )

