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ORIGINAL RESEARCH

Epidemiology and Risk Factors of Candidemia a 8-Year Retrospective Study from a Teaching Hospital in China

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Purpose: We investigated the Epidemiology, risk factors and outcomes of Candida bloodstream infection.

Methods: The electronic laboratory records data of patients with candidemia (2015–2022) were collected. We used univariate and multivariate logistic regression to determine the risk factors of candidemia.

Results: Of the 134 patients with candidemia, the most prevalent species were *Candida albicans* (37.2%), followed by *Candida glabrata* (27.7%), *Candida parapsilosis* (18.9%), and others. The mean annual incidence was 0.33/1000 admissions. The overall resistance rate of *Candida* spp. against fluconazole and voriconazole were 4.9% (7/142) and 5.9% (6/101), while *Candida tropicalis* showed high resistance to fluconazole (38.8%) and voriconazole (27.8%). The 30-day mortality rate was 32.8%. On multivariate analysis, age ≥ 65 (odds ratio [OR] = 3.874, 95% confidence interval [CI]: 1.146, 13.092; $P = 0.029$), high Acute Physiology and Chronic Health Evaluation II (APACHE II) score (OR = 12.384, 95% CI: 2.963, 51.762; $P = 0.001$), shock (OR = 3.428, 95% CI: 1.097, 10.719; $P = 0.034$), initial antifungal therapy (OR = 0.057, 95% CI: 0.011, 0.306; $P = 0.001$) and White blood cells (OR = 1.129, 95% CI: 1.016, 1.255; $P = 0.024$) were the independent risk factors with mortality within 30 day in patients with candidemia.

Conclusion: The incidence rate and the mortality rate of candidemia are high, and lower azole susceptibility was found in *Candida tropicalis*. Age≥65 years, Shock, high APACHE II score, Antifungal therapy and White blood cells count were independently associated with 30-day mortality.

Keywords: Candidemia, Epidemiology, Antifungal susceptibility, Mortality, Risk factors

Introduction

Candidemia is a common healthcare-associated bloodstream infection that leads to longer hospital stays, increased healthcare costs, and high mortality rate.[1–3] The hospital days increased from 4.1 to 5.5 days, and the medical costs increased from $10,755 to $14,479 per patient attributed to Candidemia, when compared with Gram-negative bacterial bloodstream infection.[4] The mortality rate within 30 days among patients with Candida bloodstream infection was 25.6–56.7%.[5–7]

Among *Candida* spp, *Candida albicans* is reported in a high proportion worldwide, but a shift towards *non-albicans Candida* spp. has been observed.[8] A recent systematic study in China reported the similar conclusions.[9]

Some literatures had shown that the complicated surgery, hemodialysis, prolonged use of central venous catheters (CVC), administration of total parenteral nutrition (TPN), undergoing mechanical ventilation, immunosuppressive therapies (eg chemotherapy, corticosteroids), and exposure to broad-spectrum antibacterial agents, neutropenia, prior fungal colonization and intensive care unit (ICU) admission were the risk factors for candidemia.[10–13] Several retrospective studies suggested that ICU admission, underlying diseases and comorbidities, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, multiple invasive interventions and treatments were associated with increased mortality.[11,14–16]

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The forming of biofilms for *Candida* spp. is a crucial virulence factor, which can significantly reduce its susceptibility to antifungal drugs and weakens the host immune response, which makes candidemia a great threat to the Public Health System with serious outcomes.[17,18] Due to the lack of specific clinical manifestations, early diagnosis and treatment are usually absent. However, the species distribution and susceptibility patterns of candidemia can vary with geographic region and time. Therefore, the local epidemiology, variable antifungal susceptibility and the potential risk factors of mortality are critical for appropriate antifungal therapy and treatment measures.

In this study, we retrospectively analyzed the epidemiology, clinical characteristics, species distribution of infection and antifungal drug susceptibility from 148 patients with candidemia at our hospital between 2015 and 2022. And we aimed to identify the potential risk factors associated with 30-day mortality in candidemia patients.

Material and Methods

Patients and Study Design

A single-center, retrospective observational study was undertaken from 1 January 2015 to 31 December 2022 at the Beijing Shijitan Hospital with over 1000 beds currently. The study was done in patients with culture-confirmed candidemia, the clinical data were collected from the electronic records. And the study was approved by the ethics committees of the Beijing Shijitan Hospital (Grant No. 2019–29). Since all the data were obtained from the hospital laboratory as routine work and not for this study, the informed consent was waived by the ethics committee. Patient details were anonymized before data analysis. And the research was conducted in accordance with the Declaration of Helsinki.

Definitions

An episode of candidemia was defined as the isolation of a *Candida* spp. from at least one blood culture in a patient presenting with clinical signs and symptoms. The onset of candidemia was defined as the day, when the first positive blood culture for *Candida* spp. was drawn from the patient. With the exception of recent surgery (surgery within 3 months), the predisposing factors occurred within 30 days prior to the onset of candidemia. Antifungal therapy is defined as empiric treatment (preferred azole agents) that is initiated before the patient has obtained the results of a drug susceptibility test. The severity of illness was assessed by APACHE II score. The outcome was registered after 30 days from the onset of candidemia.

Microbiological Procedures and Antifungal Susceptibility Testing

Blood samples were cultured with Bactec-9120 and Bactec-FX200 systems (Becton Dickinson, Sparks, MD). Positive blood cultures were plated on the Columbia blood and Sabouraud Dextrose agar, and then incubated aerobically at 37°C for up to 48 h. *Candida* species were identified by VITEK-2 Compact system (bioMerieux, Marcyl'Etoile, France) or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Microflex LT, Bruker Daltonics, Bremen, Germany). And the antifungal susceptibility test for fluconazole and voriconazole was determined by the ATB FUNGUS 3 (BioMérieux) strip following the manufacturer's instructions. The susceptibility to fluconazole and voriconazole was evaluated according to the clinical breakpoints of the Clinical Laboratory Standards Institute M60.[19]

Statistical Analysis

The SPSS statistical software (ver. 24.0, SPSS Inc., Chicago, IL, USA) was used to analyze the data. The continuous variables are presented as the median ± standard deviation (SD); categorical variables are expressed as a number and percentages. For continuous variables, we used Student's *t*-test, and Chi-square test or Fisher exact test was used for categorical variables. Using the Kaplan–Meier survival analysis, we compared the patients receiving and not receiving antifungal therapy. Multiple logistic regressions were performed to determine independent risk factors associated with mortality within 30 days. $P \leq 0.05$ was considered statistically significant.

Results

Study Participants and Incidence Rates

During the entire study period, a total of 148 episodes of candidemia were identified. 14 episodes were excluded, because of insufficient clinical information. Thus, 134 episodes were used to estimate the risk of candidemia in the hospital. The total candidemia incidence rate was 0.33 cases per 1000 admissions. We found a rise in candidemia incidence from 2015 to 2022 (from 0.21 to 0.48), except for 2021 (Figure 1).

Species Distribution

The *Candida albicans* (55/148; 37.2%) was the most common species causing candidemia, followed by *Candida glabrata* (41/148, 27.7%), *Candida parapsilosis* (28/148, 18.9%), *Candida tropicalis* (18/148, 12.2%), and other *Candida* spp. (6/148, 4.1%). More than half of all the isolates were *Candida non-albicans* species. And *Candida glabrata* accounted for 44.1% of non-albicans species. The trend in the *Candida* spp. distribution of candidemia from 2015 to 2022 is shown in Figure 2.

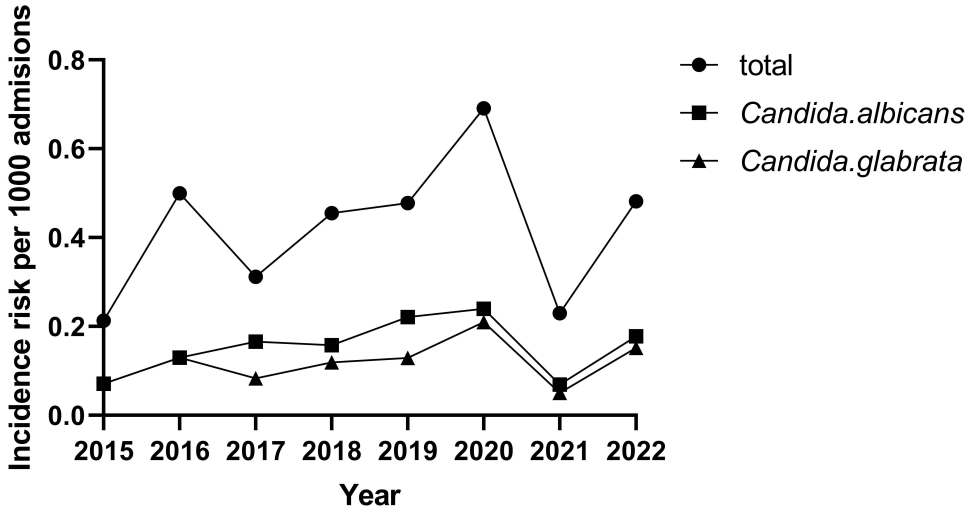

Figure 1 Annual change in incidence risk per 1000 hospital admissions of candidemia, 2015–2022. The figure showed the change in the total incidence of candidemia and the incidence rate of two major types of candidemia in our study.

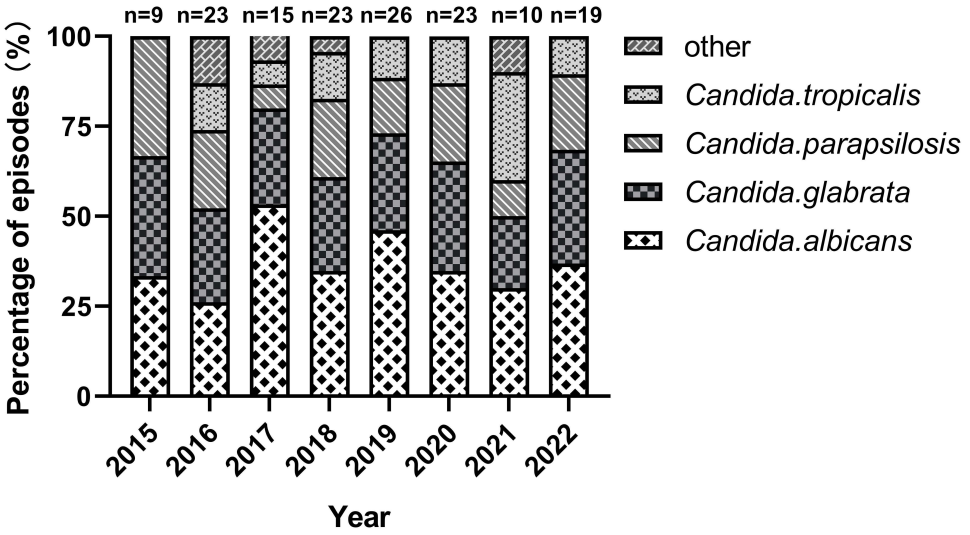

Figure 2 Distribution of *Candida* species isolates, 2015–2022. The most prevalent species was Candida albicans, followed by Candida glabrata, Candida parapsilosis, Candida tropicalis and others *Candida* spp.

Antifungal Susceptibility Testing

A total of 142 isolates were tested for the susceptibility to fluconazole and voriconazole (Table 1). Isolates identified as *Candida famata* (n = 2), *Candida lusitaniae* (n = 2), *Candida guilliermondii* (n=1), and *Candida dubliniensis* (n = 1) were excluded from this analysis, because of the lack of specific clinical breakpoints. The resistance rates of *Candida* spp. strains against fluconazole and voriconazole were 4.9% (7/142) and 5.9% (6/101), respectively. *Candida tropicalis* strains showed high resistance to fluconazole (7/18, 38.8%) and voriconazole (5/18, 27.8%). The susceptibility to fluconazole for *Candida albicans, Candida glabrata* and *Candida parapsilosis* strains was high, and no fluconazole resistant isolate was found. *Candida albicans* and *Candida parapsilosis*strains showed the most susceptible to voriconazole, and only one *Candida albicans* isolate showed voriconazole resistance.

Clinical Characteristics of Patients with Candidemia

A total of 134 patients were included in the analysis. And the 30-day mortality rate was 32.8% (44/134). The basic characteristics of patients and their outcomes are shown in Table 2. The mean age of all patients was 66.8 years (range, 1–100 years) and elderly patients (age ≥ 65) accounted for 56.0% of the sample. And 58.2% (78/134) of these patients were male. The mean hospital staying time of these patients before the occurrence of candidemia was 41.9 ± 54.4 days. For the underlying diseases, a high proportion was enumerated for solid tumor (65.7%), followed by pulmonary disease (53.7%), cardiovascular disease (49.3%), diabetes mellitus (35.1%), neurologic diseases (23.1%) and shock (23.1%). The median APACHE II score was 16.9 ± 8.3. CVC (132/134, 98.5%) was the most common invasive procedure, followed by TPN (100/134, 74.6%) and urinary catheter (89/134, 66.4%). Before the candidemia was detected,133 (99.3%) of these patients had broad-spectrum antibiotic use. When candidemia is detected, 114 (85.1%) of these patients started to take the appropriate antifungal therapy.

Table 1 Antifungal Susceptibility of Candida Spp. Isolated

	S (%)	SDD/I (%)	R (%)
C. albicans (n=55)			
Fluconazole	94.5	5.5	0.0
Voriconazole	98.2	0.0	1.8
C. glabrata (n=41)			
Fluconazole	0.0	100.0	0.0
Voriconazole	NA	NA	NA
C. parapsilosis (n=28)			
Fluconazole	96.4	3.6	0.0
Voriconazole	100.0	0.0	0.0
C. tropicalis (n=18)			
Fluconazole	55.6	5.6	38.8
Voriconazole	72.2	0.0	27.8

Abbreviations: S, susceptible; SDD/I, susceptible dose-dependent/intermediate; R, resistant; NA, non-applicable.

Table 2 Overall Characteristics and Univariate Analysis of Mortality in Patients with Candidemia

Variables	Total n = 134 (%)	Death n = 44 (%)	Survived n = 90 (%)	p value
Age, years				
≥65	75 (56.0)	35 (79.5)	40 (44.4)	<0.001
<65	59 (44.0)	9 (20.5)	50 (55.6)	
Gender				
Male	78 (58.2)	29 (65.9)	49 (54.4)	0.206
Female	56 (41.8)	15 (34.1)	41 (45.6)	
Hospital stay, days, mean±SD	41.9±54.4	40.6±46.6	42.5±58.0	0.853
Underlying diseases				
Pulmonary disease	72 (53.7)	30 (68.2)	42 (46.7)	0.019
Cardiovascular disease	66 (49.3)	27 (61.4)	39 (43.3)	0.050
Diabetes mellitus	47 (35.1)	23 (52.3)	24 (26.7)	0.004
Chronic liver disease	4 (3.0)	0 (0.0)	4 (4.4)	0.302
Chronic kidney disease	24 (17.9)	11 (25.0)	13 (14.4)	0.135
Solid tumor	88 (65.7)	27 (61.4)	61 (67.8)	0.539
Neurologic diseases	31 (23.1)	11 (25.0)	20 (22.2)	0.720
Shock	31 (23.1)	23 (52.3)	8 (8.9)	<0.001
APACHE II score, mean±SD	16.9±8.3	23.5±8.2	13.7±6.3	<0.001
Invasive Procedure				
Abdominal surgery	68 (50.7)	18 (40.9)	50 (55.6)	0.111
Central venous catheter	132 (98.5)	44 (100.0)	88 (97.8)	1.000
Mechanical ventilator	34 (25.4)	14 (31.8)	20 (22.2)	0.231
Urinary catheter	89 (66.4)	33 (75.0)	56 (62.2)	0.141
Body cavity drainage tube	49 (36.6)	15 (34.1)	34 (37.8)	0.677
Total parenteral nutrition	100 (74.6)	32 (72.7)	68 (75.6)	0.724
Before candidemia				
Broad-spectrum antibiotic use	133 (99.3)	43 (97.7)	90 (100.0)	0.328
Corticosteroid use	73 (54.5)	23 (52.3)	50 (55.6)	0.720
After candidemia				
Antifungal therapy	114 (85.1)	29 (65.9)	85 (94.4)	0.001
Laboratory findings				
C-reactive protein (mg/L), mean±SD	89.2±62.8	107.0±75.3	80. 6±54.1	0.021
Procalcitonin (ng/L), mean±SD	14.1±31.9	21.4±40.1	10.4±26.3	0.069

(*Continued*)

Table 2 (Continued).

Variables	Total n = 134 (%)	Death n = 44 (%)	Survived n = 90 (%)	p value
Albumin (g/l), mean±SD	36.8±38.5	39.5±64.2	35.5±14.6	0.571
White blood cells (×109/L), mean±SD	9.3±5.4	11.7±6.3	8.2±4.5	<0.001

Abbreviations: SD, standard deviation; APACHE II, Acute Physiology and Chronic Health Evaluation II; CVC, Central venous catheter; TPN, Total parenteral nutrition.

Risk Factors for Mortality from Candidemia

We used the univariate analysis to screen the risk factors of candidemia (Table 2). Age ($P < 0.001$), pulmonary disease ($P = 0.019$), diabetes mellitus ($P = 0.004$), shock ($P < 0.001$), APACHE II score ($P < 0.001$), antifungal therapy ($P = 0.001$), C-reactive protein ($P = 0.021$) and White blood cells ($P < 0.001$) were significantly related to mortality.

Furthermore, patients receiving and not receiving antifungal therapy was compared by Kaplan–Meier survival analysis ($P < 0.001$) (Figure 3).

By multivariate logistic regressions analysis, five independent risk factors for candidemia related 30-day mortality were identified: age ≥ 65 (odds ratio [OR] = 3.874; 95% confidence interval [CI]: 1.146, 13.092; $P = 0.029$), high APACHE II score (OR = 12.384; 95% CI: 2.963, 51.762; $P = 0.001$), shock (OR = 3.428; 95% CI:1.097, 10.719; $P = 0.034$), antifungal therapy (OR = 0.057; 95% CI: 0.011, 0.306; $P = 0.001$) and White blood cells (OR = 1.129; 95% CI: 1.016, 1.255; $P = 0.024$) (Table 3).

Discussion

In this single-center retrospective study, the clinical characteristics of candidemia episodes of a tertiary-care hospital in the past 8 years were analyzed. The incidence rate was 0.33 cases per 1000 admissions, which was similar to a study,[20] higher than another Chinese report.[21] We also found that the incidence rate has increased in these years, consistent with the reported studies.[6,22]

In addition, the species distribution pattern of candidemia varies greatly in different regions of the world. 37.2% of isolated species in our study period were *Candida albicans*, followed by *Candida glabrata, Candida parapsilosis, Candida tropicalis*, similar with reports from other regions.[21,23,24] However, some Chinese studies showed different

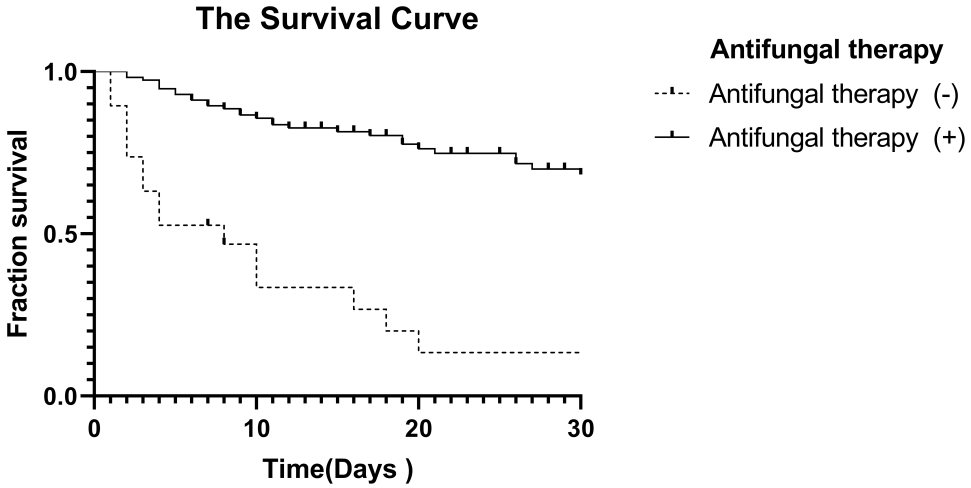

Figure 3 Kaplan–Meier survival analysis for candidemia. Patients treated with antifungal drugs and patients not treated with antifungal drugs were included (p<0.001).

Table 3 Multivariate Analysis of Factors Associated with 30-Day Mortality in Patients with Candidemia

Factor	OR (95% CI)	P
Age≥65	3.874 (1.146, 13.092)	0.029
Shock	3.428 (1.097, 10.719)	0.034
APACHE II	12.384 (2.963, 51.762)	0.001
Antifungal therapy	0.057 (0.011, 0.306)	0.001
White blood cells	1.129 (1.016, 1.255)	0.024

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; OR, odds ratio; CI, confidence interval.

results, the incidence of *Candida tropicalis*[6] rather than *Candida albicans* ranked first in leading candidemia according to their observation.

During the past 20 years, increased drug resistance of *Candida* spp. to azoles has attracted the attention from the world. In our hospital, only three *Candida albicans* isolates (5.5%) and one *Candida parapsilosis* (3.6%) showed intermediate susceptibility. *Candida albicans* and *Candida parapsilosis* exhibited excellent susceptibility (>98.0%) to voriconazole, and only one *Candida albicans* isolate showed voriconazole resistance. These results were similar with previously reports.[6,24] But high resistance to fluconazole of *Candida glabrata* have been reported from the studies conducted in the European and American countries.[25] The *Candida tropicalis* isolates in our study had 38.8% resistance to fluconazole and 27.8% resistance to voriconazole. The frequency of fluconazole resistance was only 20.5% in an Australian study.[26] But our result is consistent with the findings of other Chinese studies.[5,6,27] The rapid emergence of azole-resistant *Candida tropicalis* strains was also revealed in China CHIF-NET surveillance.[28] So, azoles may be not the appropriate antifungal drugs for empirical treatment of *Candida tropicalis*, which is consistent with other reports.[29,30]

High mortality are associated with candidemia. In our study, the 30-day mortality rate of candidemia was 32.8%, which is consistent with some previous reports,[31–33] but lower than these studies[22,34] and higher than other Chinese reports.[5,6]

Univariate analysis revealed that age ≥ 65 years, pulmonary disease, diabetes mellitus, shock, high APACHE II score, antifungal therapy, C-reactive protein and White blood cells count were the factors that affected the mortality within 30 days. However, age ≥ 65 years, shock, high APACHE II score, antifungal therapy and White blood cells count were the independent risk factors of 30-day mortality from candidemia in our study. Consistent with our results, previous studies showed that age ≥ 65 years could be the predictors of high mortality.[32,35] Because of low immunity, chronic diseases, and multi-organ failure, elderly patients were susceptible to candidemia. Given rapidly aging societies, age ≥ 65 maybe a more predictive risk factor for mortality in cases with candidemia. Moreover, our study showed that shock was significantly associated with 30-day mortality after candidemia diagnosis. And shock may be considered to be significant predictors for mortality by affecting immunity.[22,36] Several previous studies support our findings that a high APACHE II score also can be used as a predictor of high mortality in patients with candidemia.[37–39] Our results revealed that the use of appropriate antifungal agents in patients with candidemia is a protective factor, and some studies showed the similar result.[40,41] In addition, the finding that White blood cells count is an independent significant predictor of mortality in patients with candidemia is consistent with some studies.[33,42] But some studies have had different results: they found that TPN, exposure to broad-spectrum antibacterial agents, Hemodialysis, and arteriovenous catheter were associated with an increased risk of mortality.[33,43]

Several limitations have showed in our study. First, it was a retrospective study, which might have lead to selection and observational bias and affected the results. Second, it was a single center study, which might have a small sample size and limited information, and then might impact the analysis results. Third, we did not perform the in vitro echinocandin susceptibility test of *Candida* isolates.

Conclusion

In conclusion, in this 8-year study, the incidence rate of candidemia seemed to have increased, and *Candida albicans* was the most frequently isolated species. We also found that *Candida tropicalis* had significantly lower azole susceptibility, so empirical treatment would not recommend using azoles. Moreover, patients with candidemia showed high mortality rate. In our study, we identified five independent risk factors for 30-day mortality in patients with candidemia: age ≥ 65 years, shock, high APACHE II score, antifungal therapy and White blood cells count. In order to further assess the changing epidemiology of candidemia, multi-center prospective studies may be required in future.

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Disclosure

The authors declare that there are no conflicts of interest in this article.

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