

## ORIGINAL ARTICLE

# Epidemiology and antifungal susceptibility of candidemia isolates of non-*albicans* *Candida* species from cancer patients

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Candidemia is a growing concern worldwide, and its species distribution has shifted toward non-*albicans* *Candida* in recent decades, especially in patients with malignancy. This study aimed to update the epidemiology and antifungal susceptibility of non-*albicans* candidemia isolates from the cancer patients. Adult cancer patients with non-*albicans* candidemia were recruited, and clinical data were retrospectively collected from five medical centers in Taiwan from 1 July 2011 to 30 June 2014. *In vitro* susceptibility was determined by the broth dilution method using a Sensititre YeastOne system and interpreted according to the guidelines of the Clinical and Laboratory Standards Institute. A total of 346 episodes of non-*albicans* candidemia were identified in cancer patients. *Candida tropicalis* was the most common species ( $n = 145$ , 41.9%) and had the highest resistance rate to fluconazole ( $n = 17$ , 13.9%) among all the preserved isolates, including *C. tropicalis*, *Candida glabrata* and *Candida parapsilosis*. A higher Charlson comorbidity index, non-*albicans* candidemia due to *C. tropicalis*, neutropenia and septic shock were independent predictors of 28-day mortality. In conclusion, the species distribution and antifungal susceptibility of non-*albicans* candidemia isolates in our study differed from those in Western countries, providing useful information about local epidemiology for the selection of empirical antifungal agents for cancer patients.

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## INTRODUCTION

*Candida* species have become increasingly important pathogens in healthcare settings worldwide. In 2004, candidemia was reported as the fourth to sixth leading cause of nosocomial bloodstream infections in Western countries, including in the United States and Switzerland.<sup>1,2</sup> A more recent multicenter study in 2014 that enrolled 183 hospitals in the United States showed that candidemia was the most common etiology of healthcare-associated bloodstream infections.<sup>3</sup> In Taiwan, the incidence of candidemia has also shown an increasing trend, from 0.8 patients per 10 000 discharges in 1981 to 28.8 patients per 10 000 discharges in 2000.<sup>4</sup> Furthermore, the species distribution of candidemia varies geographically and has changed in recent decades. The proportion of different species causing candidemia has shifted toward non-*albicans* *Candida* species; *Candida tropicalis* and *Candida parapsilosis* are prominent in Taiwan and China, respectively,<sup>5–7</sup> and *Candida glabrata* is prominent in the United States.<sup>8,9</sup>

Malignancy is a major underlying comorbidity of patients with candidemia. For cancer patients, candidemia is associated with a high mortality rate (30%–50%) that results in substantial healthcare costs and prolonged hospital stays.<sup>10–13</sup> Recent literature has shown that despite the introduction of novel antifungal agents, candidemia in cancer patients remains a severe disease with a high mortality rate of 31–68%.<sup>6,14–16</sup> Candidemia caused by fluconazole-resistant strains, which are composed exclusively of non-*albicans* *Candida* species, has been shown to significantly increase mortality among patients with solid organ or hematological malignancies.<sup>14</sup> Furthermore, previous studies have reported that the contribution of non-*albicans* *Candida* species to candidemia in cancer patients is increasing.<sup>16–18</sup> Hence, an understanding of the epidemiology of non-*albicans* candidemia and the antifungal susceptibilities of these isolates is currently imperative to guide optimal empirical treatment strategies for affected patients.

In this report, we conducted a multicenter study to determine the clinical characteristics and antifungal susceptibilities of non-*albicans*

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candidemia in cancer patients and to identify the potential risk factors associated with 28-day mortality.

## MATERIALS AND METHODS

### Setting and study design

This multicenter study was conducted at the Taipei Veterans General Hospital with 2900 beds in northern Taiwan, Chi Mei Hospital with 900 beds in southern Taiwan, Kaohsiung Medical University Hospital with 1600 beds in southern Taiwan, China Medical University Hospital with 2111 beds in central Taiwan and Changhua Christian Hospital with 1487 beds in central Taiwan. All adult cancer patients older than 20 years of age, with a bloodstream infection due to non-*albicans Candida*, and who were admitted to any of the above-mentioned five medical centers between 1 July 2011 and 30 June 2014 were enrolled in the study. In the case of patients who suffered two or more episodes of non-*albicans* candidemia during the study period, only the first episode was included in our analysis. Patients with a bloodstream infection caused by two or more *Candida* species were excluded. Non-*albicans Candida* isolates obtained from patients at the enrolled hospitals were analyzed for antifungal susceptibility at a medical center.

The medical records of all enrolled patients were reviewed by infectious disease specialists, and the variables collected from medical charts were as follows: age, gender, Charlson comorbidity index, underlying comorbidities, cancer types, origin of non-*albicans* candidemia, underlying conditions (use of a central venous catheter, recently received chemotherapy, total parenteral nutrition, steroid, proton-pump inhibitor and abdominal surgery, and prior exposure to broad-spectrum antibiotics), severity of illness (neutropenia and septic shock), concomitant bacterial infections, antifungal therapy and 28-day outcome. This study was approved by the Medical Ethics Committees of the five enrolled hospitals.

### Definitions

Patients infected with non-*albicans* candidemia were confirmed by at least one set of positive blood cultures and compatible clinical symptoms and signs.<sup>19</sup> The origin of the candidemia was identified as the site from which the same non-*albicans Candida* species was isolated. Catheter-related bloodstream infection (CRBSI) was defined by semi-quantitative tip culture as the growth of  $\geq 15$  colonies that were identical to the species identified from the peripheral blood culture.<sup>20</sup> Primary candidemia was defined as a non-*albicans* candidemia occurring in the absence of an apparent portal of entry. Healthcare-associated infection was determined according to the criteria provided by the Centers for Disease Control and Prevention, USA.<sup>21</sup> Recent abdominal surgery, the recent use of steroids (at least 10 mg of prednisolone or an equivalent daily dosage for more than 7 days), broad-spectrum antibiotics or proton-pump inhibitors were defined as undergoing interventions or agents when they occurred within 30 days before the positive blood culture. Chemotherapy received within 90 days before the infection was defined as 'recently received chemotherapy'. Neutropenia was indicated by an absolute neutrophil count of  $< 500 \times 10^6$  cells per liter, and septic shock was defined by a systolic pressure below 90 mm Hg and a need for vasopressors. Antifungal therapy was determined based on the predominant agent, which was used for most of the duration of the treatment course. The 28-day mortality values were identified based on the medical records of the five enrolled hospitals, including the discharge day before 28 days from the onset of non-*albicans* candidemia.

### Microbiological analysis of non-*albicans Candida* isolates

All preserved, available non-*albicans Candida* isolates were identified by morphology analysis on CHROMagar (Creative Life Science, New Taipei City, Taiwan) and biochemical methods using a Vitek 2 system with the YST Card (bioMérieux, Durham, NC, USA). The broth microdilution method using a Sensititre YeastOne system (Trek Diagnostic Systems, East Grinstead, UK) was performed to determine the minimum inhibitory concentration (MIC) according to the manufacturer's instructions. *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 were used as quality control strains. The MICs of amphotericin B, caspofungin, micafungin, anidulafungin, fluconazole, voriconazole, itraconazole, posaconazole and flucytosine were determined, and interpretation criteria were based on the MIC breakpoints of non-*albicans Candida* species, as recommended by the Clinical and Laboratory Standards Institute.<sup>22</sup>

### Statistical analyses

Statistical analyses were performed using SPSS software version 17 (SPSS, Chicago, IL, USA). Categorical data were compared using  $\chi^2$  or Fisher's exact tests. Continuous data were analyzed using Student *t*-test or Mann-Whitney *U* test. Statistical significances were determined using two-tailed tests, and a value of  $P < 0.05$  was considered significant. Logistic regression analysis was used to identify the independent predictors of 28-day mortality. All biologically plausible variables with values of  $P < 0.10$  in univariate testing were included in the model.

## RESULTS

During the study period, 346 episodes of candidemia caused by non-*albicans Candida* were identified in a study population of 346 patients. No significant differences were observed in the proportions of candidemia caused by different non-*albicans Candida* species each year ( $P = 0.489$ ). In addition, Figure 1 shows the species ratio trends of non-*albicans* candidemia cases from 2011 to 2014. Table 1 summarizes the demographics and clinical data of the patients with non-*albicans* candidemia enrolled in the study. The study population included 221 (63.9%) male and 125 (36.1%) female participants, and the mean age of all patients enrolled was  $63.9 \pm 15.4$  years old. Gastrointestinal cancer was the most common malignancy in patients with non-*albicans* candidemia enrolled in the study (160 patients, 46.2%). Apart from malignancy, 168 (48.6%) patients had other underlying comorbidities; diabetes mellitus (107 patients, 30.9%) was the most frequent disease among these conditions. CRBSI (108 patients, 31.2%)

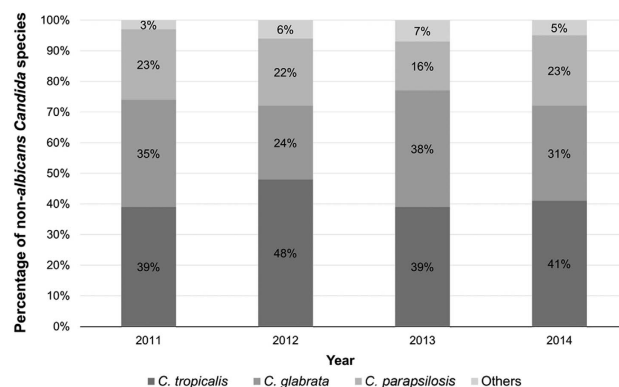


Figure 1 Trend in species distribution of non-*albicans* candidemia from 2011 to 2014.

**Table 1 Demographics and clinical characteristics of cancer patients with non-*albicans* candidemia**

Characteristic	Number of patients (%)
Gender, male	221 (63.9)
Age, years	63.9 ± 15.4
Age ≥ 65 years	165 (47.7)
Charlson comorbidity index	5.6 ± 2.8
<i>Underlying comorbidities</i>	
Diabetes mellitus	107 (30.9)
Cerebrovascular accident	24 (6.9)
Congestive heart failure	18 (5.2)
End-stage renal disease	14 (4)
Liver cirrhosis	26 (7.5)
Chronic lung disease	36 (10.4)
<i>Type of cancer</i>	
Head and neck cancer	58 (16.8)
Lung cancer	22 (6.4)
Gastrointestinal cancer	160 (46.2)
Genitourinary cancer	40 (11.6)
Breast cancer	15 (4.3)
Hematological malignancy	46 (13.3)
Others <sup>a</sup>	7 (2)
<i>Non-<i>albicans</i> <i>Candida</i> species</i>	
<i>C. tropicalis</i>	145 (41.9)
<i>C. glabrata</i>	111 (32.1)
<i>C. parapsilosis</i>	70 (20.2)
<i>C. krusei</i>	7 (2)
<i>C. guilliermondii</i>	5 (1.4)
<i>C. sake</i>	2 (0.6)
<i>C. dubliniensis</i>	2 (0.6)
<i>C. lipolytica</i>	1 (0.3)
<i>C. lusitanae</i>	1 (0.3)
<i>C. norvegensis</i>	1 (0.3)
<i>C. famata</i>	1 (0.3)
<i>Origin of non-<i>albicans</i> candidemia</i>	
Primary infection	136 (39.3)
Catheter-related infection	108 (31.2)
Urinary tract infection	29 (8.4)
Respiratory tract infection	42 (12.1)
Intra-abdominal infection	29 (8.4)
Skin and soft tissue infection	2 (0.6)
<i>Underlying conditions</i>	
Presence of central venous catheter	294 (85)
Presence of Foley catheter	127 (36.7)
Chemotherapy	168 (48.6)
Total parental nutrition	96 (27.7)
Steroid	119 (34.4)
Proton-pump inhibitor	145 (41.9)
Abdominal surgery	58 (16.8)
Prior exposure to broad-spectrum antibiotics	306 (88.4)
Neutropenia	21 (6.1)
Septic shock	124 (35.8)
Concomitant bacterial infections	127 (36.7)

**Table 1 (Continued)**

Characteristic	Number of patients (%)
<i>Antifungal therapy</i>	
Amphotericin B	5 (1.4)
Triazole	192 (55.5)
Echinocandin	102 (29.5)
None	47 (13.6)
Length of hospital stay after infection (days)	22.1 ± 20.4
28-day mortality	154 (44.5)

Data are presented as mean ± standard deviation (s.d.) or frequency with percentage (%).  
<sup>a</sup>Others included glioblastoma multiforme, peritoneal mesothelioma, retroperitoneal carcinoma, skin cancer and malignancy of unknown origin.

accounted for the most commonly identified origin of non-*albicans* candidemia, and 136 (39.3%) episodes were classified as primary infection. The presence of a central venous catheter (294 patients, 85%) and prior exposure to broad-spectrum antibiotics (306 patients, 88.4%) were the most common risk factors associated with non-*albicans* candidemia in this study. The majority of predominant antifungal agents were triazoles (192 patients, 55.5%). Across the study population, only 29 (8.4%) and 83 (24%) patients ever received prophylactic or empirical antifungal therapies, respectively. In addition to the patients undergoing prophylactic or no treatment, the median (interquartile range) duration of prescribed antifungal agents after collecting index blood cultures was two (0.20–3.18) days.

Table 2 shows the distribution and frequency of non-*albicans* *Candida* species isolated from patients with different types of cancers. *C. tropicalis* was the major cause of non-*albicans* candidemia in all patients, regardless of cancer type. However, no significant differences were observed in the distribution of non-*albicans* *Candida* species among the five major cancer categories analyzed. Notably, when patients with solid organ malignancies were compared with those with hematological cancers, non-*albicans* candidemia caused by *C. tropicalis* was significantly higher in patients with hematological malignancies (58.7% versus 39.3%,  $P=0.020$ ).

A total of 251 non-*albicans* candidemia isolates were available for the antifungal susceptibility test, as shown in Table 3. Of these non-*albicans* candidemia-causative isolates, 22 (8.8%) were resistant to *in vitro* fluconazole, including 17 *C. tropicalis*, 3 *C. glabrata* and 2 *C. parapsilosis* isolates. Although *C. tropicalis* showed the highest rate of resistance to fluconazole (13.9%) among the preserved isolates, *C. glabrata* exhibited the highest fluconazole MIC<sub>50</sub> and MIC<sub>90</sub> (16 mg/L and 32 mg/L, respectively) among all non-*albicans* *Candida* species. The overall susceptibility rates for echinocandins were high (>90%), except for caspofungin in *C. glabrata* (83.3%) isolates. The echinocandin MIC<sub>50</sub> and MIC<sub>90</sub> of *C. parapsilosis* (0.5–1 mg/L and 0.5–2 mg/L) were higher than other non-*albicans* *Candida* species, but all *C. parapsilosis* isolates were susceptible to three echinocandins.

The overall 28-day mortality rate in this study was 44.5% (154 patients). Moreover, the mortality rates among the three most common non-*albicans* *Candida* species, *C. tropicalis*, *C. glabrata* and *C. parapsilosis*, were 53.8% (78 out of 145 patients), 40.5% (45 out of 111 patients) and 31.4% (22 out of 70 patients), respectively. To identify the independent risk factors associated with 28-day mortality in cancer patients with non-*albicans* candidemia, we stratified the 346 patients into survival and death groups (Table 4). In the univariate analysis, patients with a higher Charlson comorbidity index

**Table 2** Distribution and frequency of non-*albicans* *Candida* species in patients with different types of cancers

Species	Number of isolates (%)				
	Head and neck cancer	Gastrointestinal tract cancer	Lung cancer	Genitourinary cancer	Hematological cancer
<i>C. tropicalis</i>	26 (44.8)	62 (38.8)	10 (45.5)	16 (40)	27 (58.7)
<i>C. glabrata</i>	14 (24.1)	60 (37.5)	6 (27.3)	14 (35)	10 (21.7)
<i>C. parapsilosis</i>	17 (29.3)	29 (18.1)	6 (27.3)	8 (20)	4 (8.7)
<i>C. krusei</i>	0 (0)	3 (1.9)	0 (0)	0 (0)	3 (6.5)
<i>C. guilliermondii</i>	0 (0)	3 (1.9)	0 (0)	2 (5)	0 (0)
Others <sup>a</sup>	1 (1.7)	3 (1.9)	0 (0)	0 (0)	2 (4.3)

Data are presented as frequency with percentage (%).

<sup>a</sup>Other species included *C. sake*, *C. lusitanae*, *C. lipolytica*, *C. norvegensis*, *C. famata* and *C. dubliniensis*.

**Table 3** *In vitro* activities of antifungal agents tested against 251 non-*albicans* *Candida* isolates obtained from patients with candidemia according to the Clinical and Laboratory Standards Institute recommendations

Non- <i>albicans</i> <i>Candida</i> species	MIC range (mg/L)	MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)	Number of isolates (%)			
				S	SDD	I	R
<i>C. tropicalis</i> (n = 122)							
Amphotericin B	0.25–2	0.5	1	—	—	—	—
Fluconazole	0.25–128	2	8	87 (71.3)	18 (14.8)	—	17 (13.9)
Voriconazole	0.015–4	0.25	1	60 (49.2)	49 (40.2)	—	13 (10.7)
Posaconazole	0.015–2	0.25	0.5	—	—	—	—
Itraconazole	0.06–1	0.25	0.5	—	—	—	—
Caspofungin	0.015–>8	0.06	0.25	118 (96.7)	—	1 (0.8)	3 (2.5)
Micafungin	0.015–2	0.03	0.03	118 (96.7)	—	1 (0.8)	3 (2.5)
Anidulafungin	0.03–1	0.12	0.25	119 (97.5)	—	1 (0.8)	2 (1.6)
Flucytosine	≤0.06–>64	≤0.06	0.12	—	—	—	—
<i>C. glabrata</i> (n = 96)							
Amphotericin B	≤0.12–4	0.5	1	—	—	—	—
Fluconazole	0.5–>256	16	32	—	93 (96.7)	—	3 (3.1)
Voriconazole	≤0.008–4	0.5	1	—	—	—	—
Posaconazole	0.015–>8	1	2	—	—	—	—
Itraconazole	0.03–2	0.5	1	—	—	—	—
Caspofungin	0.03–1	0.12	0.25	80 (83.3)	—	14 (14.6)	2 (2.1)
Micafungin	≤0.008–1	0.015	0.015	90 (93.8)	—	1 (1)	5 (5.2)
Anidulafungin	≤0.015–1	0.06	0.12	90 (93.8)	—	1 (1)	5 (5.2)
Flucytosine	≤0.06–0.5	≤0.06	0.12	—	—	—	—
<i>C. parapsilosis</i> (n = 33)							
Amphotericin B	0.25–1	0.5	0.5	—	—	—	—
Fluconazole	0.25–8	1	2	30 (90.9)	1 (3)	—	2 (6.1)
Voriconazole	≤0.008–0.25	0.015	0.03	32 (97)	1 (3)	—	0 (0)
Posaconazole	0.015–0.12	0.03	0.06	—	—	—	—
Itraconazole	0.03–0.25	0.06	0.12	—	—	—	—
Caspofungin	0.25–1	0.5	0.5	33 (100)	—	0 (0)	0 (0)
Micafungin	0.25–2	1	2	33 (100)	—	0 (0)	0 (0)
Anidulafungin	0.25–2	1	2	33 (100)	—	0 (0)	0 (0)
Flucytosine	≤0.06–0.5	0.12	0.25	—	—	—	—

Abbreviations: intermediate, I; minimum inhibitory concentrations for 50% and 90% of the organisms, respectively, MIC<sub>50/90</sub>; susceptible, S; susceptible dose-dependent, SDD; resistant, R. Data are presented as frequency with percentage (%).

( $P=0.011$ ), a non-*albicans* candidemia caused by *C. tropicalis* ( $P=0.003$ ), a primary infection ( $P=0.006$ ), neutropenia ( $P=0.005$ ) or septic shock ( $P<0.001$ ) had significantly higher 28-day mortality

rates. The results of this multivariate analysis showed that a higher Charlson comorbidity index (odds ratio (OR): 1.18; 95% confidence interval (CI): 1.08–1.30;  $P<0.001$ ), a non-*albicans* candidemia caused

**Table 4** Analysis of potential risk factors associated with 28-day mortality in patients with non-*albicans* candidemia

Variables	Survival	Death	Univariate analysis	Multivariate analysis	
	n= 192	n= 154		P-value	Odds ratio (95% CI)
Male	122 (63.5)	99 (64.3)	0.886	0.79 (0.48–1.31)	0.361
Age in years	63.8±15.3	64±15.5	0.923	0.99 (0.98–1.01)	0.381
Charlson comorbidity index	5.2±2.6	6±3	0.011	1.18 (1.08–1.30)	<0.001
Hematological malignancy	20 (10.4)	26 (16.9)	0.081	0.80 (0.35–1.82)	0.598
<i>Non-albicans Candida species</i>					
<i>C. tropicalis</i>	67 (34.9)	78 (50.6)	0.003	1.91 (1.11–3.29)	0.019
<i>C. glabrata</i>	66 (34.4)	45 (29.2)	0.308		
<i>C. parapsilosis</i>	48 (25)	22 (14.3)	0.015	0.94 (0.47–1.86)	0.858
<i>C. krusei</i>	4 (2.1)	3 (2)	0.931		
<i>C. guilliermondii</i>	3 (1.6)	2 (1.3)	0.839		
<i>C. sake</i>	2 (1)	0 (0)	0.999		
<i>C. dubliniensis</i>	0 (0)	2 (1.3)	0.999		
<i>C. lipolytica</i>	0 (0)	1 (0.7)	1.000		
<i>C. norvegensis</i>	0 (0)	1 (0.7)	1.000		
<i>C. famata</i>	1 (0.5)	0 (0)	1.000		
<i>Origin of non-albicans candidemia</i>					
Primary infection	63 (32.8)	73 (47.4)	0.006	1.37 (0.77–2.42)	0.283
Catheter-related infection	76 (39.6)	32 (20.8)	<0.001	0.58 (0.31–1.07)	0.082
Urinary tract infection	15 (7.8)	14 (9.1)	0.670		
Respiratory tract infection	23 (12)	19 (12.3)	0.919		
Intra-abdominal infection	14 (7.3)	15 (9.7)	0.416		
Skin and soft tissue infection	1 (0.5)	1 (0.6)	0.876		
<i>Underlying conditions</i>					
Presence of central venous catheter	167 (87)	127 (82.5)	0.245		
Presence of Foley catheter	66 (34.4)	61 (39.6)	0.316		
Chemotherapy	94 (49)	74 (48.1)	0.867		
Total parental nutrition	58 (30.2)	38 (24.7)	0.254		
Steroid	58 (30.2)	61 (39.6)	0.068	1.61 (0.97–2.67)	0.068
Proton-pump inhibitor	78 (40.6)	67 (43.5)	0.589		
Abdominal surgery	35 (18.2)	23 (14.9)	0.503		
Prior exposure to broad-spectrum antibiotics	169 (88)	137 (89)	0.786		
Neutropenia	5 (2.6)	16 (10.4)	0.005	3.67 (1.07–12.55)	0.038
Septic shock	50 (26)	74 (48.1)	<0.001	2.29 (1.39–3.77)	0.001
Concomitant bacterial infections	65 (33.9)	62 (40.3)	0.220		

Data are presented as mean ± standard deviation (s.d.) or frequency with percentage (%).

by *C. tropicalis* (OR: 1.91; 95% CI: 1.11–3.29;  $P=0.019$ ), neutropenia (OR: 3.67; 95% CI: 1.07–12.55;  $P=0.038$ ) and septic shock (OR: 2.29; 95% CI: 1.39–3.77;  $P=0.001$ ) were independent predictors of 28-day mortality.

## DISCUSSION

Candidemia, with a shift in species distribution towards non-*albicans Candida* species, remains a lethal disease. Moreover, malignancy is identified as the major comorbidity of patients with candidemia. Here, we report several relevant findings obtained from a large multicenter study that characterized non-*albicans* candidemia in cancer patients. In this study, *C. tropicalis* was the main cause of non-*albicans* candidemia in cancer patients. Most isolates of non-*albicans Candida* (>80%) were susceptible or susceptible dose-dependent to echinocandins and fluconazole. Non-*albicans* candidemia due to *C. tropicalis*, as well as a

higher Charlson comorbidity index, neutropenia and septic shock, were independently associated with poor prognosis.

*C. parapsilosis* has been reported to be the most common cause of non-*albicans* candidemia among patients with malignancy in Western countries, including the United States, Australia and Portugal.<sup>13,14,23</sup> In our study, the major non-*albicans Candida* species identified in cancer patients with candidemia was *C. tropicalis*, consistent with previous reports in Taiwan.<sup>6,15</sup> The clinical features of the non-*albicans Candida* species distribution of candidemia seemed more likely to be influenced by geography than by underlying comorbidities. Consequently, establishing the epidemiology at each research surveillance site is important, and *C. tropicalis* is one of the most important and predominant causes of non-*albicans* candidemia in cancer patients, especially in Taiwan. In fact, *C. tropicalis* has been identified as the leading cause of non-*albicans* candidemia in all patients with or without a diagnosed

malignancy (49.4%–35.4%) in Taiwan since the year 2000,<sup>7,20,24–26</sup> except in a study by Lin *et al.*, which enrolled a small number of patients with non-*albicans* candidemia.<sup>27</sup>

In our study, *C. tropicalis* was not only the most common cause of non-*albicans* candidemia but also the species with the highest resistance rate to fluconazole among the preserved isolates of the three non-*albicans* *Candida* species (*C. tropicalis*, *C. glabrata* and *C. parapsilosis*) analyzed. In general, *C. glabrata*, with reduced susceptibility,<sup>28</sup> and *C. krusei*, with intrinsic resistance,<sup>29</sup> were two commonly indicated non-*albicans* *Candida* species for which increasing fluconazole resistance was observed. According to the definitions set by the Clinical Laboratory Standards Institute [M27-S4],<sup>22</sup> national surveillance research in Brazil showed that none of the *C. tropicalis* isolates obtained were resistant to fluconazole, whereas 36.4% (4/11) of *C. glabrata* isolates were resistant to fluconazole. However, 96.7% (93/96) of *C. glabrata* isolates were susceptible dose-dependent to fluconazole in our study, and 86.1% (105/122) of *C. tropicalis* isolates were susceptible or susceptible dose-dependent to fluconazole. Tan *et al.*<sup>30</sup> conducted a multicenter study that characterized clinical isolates from patients with candidemia in countries in the Asia-Pacific region and reported the fluconazole susceptibility rates for *C. tropicalis* (susceptible rate=75.8%; susceptible dose-dependent rate=6.1%) and *C. glabrata* (susceptible dose-dependent rate=94.9%), which are in accordance with the results of our study. Furthermore, Yang *et al.*<sup>5</sup> reported that of the *C. glabrata* isolates obtained from patients with candidemia, none were resistant to fluconazole, but 27.8% (5/18) of *C. tropicalis* isolates were resistant to fluconazole in China. A more recent study by Chen *et al.*<sup>31</sup> reported that the resistance rate to fluconazole of *C. tropicalis* was 9.5% in patients with candidemia in Taiwan and that the resistance rates of *C. glabrata* and *C. parapsilosis* were 5.4% and 2%, respectively. Taken together, these studies imply that not only the species distribution of non-*albicans* candidemia but also the antifungal susceptibility of the causative agents differs from region to region and that *C. tropicalis* is the most fluconazole-resistant species among clinically common non-*albicans* *Candida* species causing candidemia around the Asia-Pacific region, including Taiwan.

Previous studies have reported that underlying conditions and the severity of illness, including advanced age, septic shock, neutropenia, acute respiratory failure and a high Acute Physiology and Chronic Health Evaluation (APACHE) II score, are significantly associated with mortality in cancer patients with non-*albicans* candidemia,<sup>6,13,15</sup> consistent with the results presented in this study. We further found that non-*albicans* candidemia due to *C. tropicalis* was an independent predictor of 28-day mortality. Compared with other species of non-*albicans* *Candida*, patients with *C. tropicalis* candidemia tended to present a higher severity of illness, such as neutropenia (10.3% versus 3%,  $P=0.006$ ) and septic shock (44.8% versus 29.4%,  $P=0.003$ ). These results and the relatively high resistance rate to fluconazole of *C. tropicalis*, as mentioned previously, may contribute to the poor outcome of patients with non-*albicans* candidemia due to *C. tropicalis*. In the literature, *C. tropicalis* is shown as the highest fluconazole-resistant species among the three most clinically common non-*albicans* *Candida* (*C. tropicalis*, *C. glabrata* and *C. parapsilosis*) in Asian countries,<sup>5,30,31</sup> but these studies did not investigate the impact of different non-*albicans* *Candida* species on survival in cancer patients. A population-based study in Spain conducted by Puig-Asensio *et al.*<sup>16</sup> demonstrated that candidemia caused by *C. krusei* was an independent risk factor of higher 30-day mortality in cancer patients with the use of a central venous catheter (OR: 12.59; 95% CI: 2.46–64.48;  $P=0.002$ ). This disagrees with results from our study, possibly due to different

geographies and study populations. Further large-scale, intensive research on this issue in different regions is imperatively needed.

A few limitations of the present study should be noted. First, this study was inherently retrospective in design, and thus missing values and potential information bias may have arisen. Second, APACHE II scores from the enrolled patients were not available. Septic shock and neutropenia are possible confounding factors in APACHE II scores, and therefore the frequencies of these two variables were monitored in the study to strengthen the results. Third, information about catheter removal in patients with CRBSI was unavailable, and the influence of this action on survival could not be evaluated. Finally, *in vitro* susceptibility results were only available for the preserved isolates, and appropriate or inappropriate therapy could not be defined for all of the study population. As a result, the analysis of mortality did not include the use of antifungal agents. Further research is needed to investigate the impact of antifungal therapy and catheter removal on the prognosis of patients with non-*albicans* candidemia. Despite its limitations, this is a large, multicenter study that may allow for more generalizable findings and may provide useful information for the treatment of fungal infections in cancer patients.

In conclusion, the epidemiology of non-*albicans* candidemia in cancer patients is a growing concern that must be addressed. Among cancer patients in Taiwan, *C. tropicalis* is the leading species causing non-*albicans* candidemia and is the species with the highest resistance to fluconazole among the clinically major non-*albicans* *Candida* species. Continuous monitoring of the species distribution and antifungal susceptibility of candidemia cases is necessary.

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