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# Poor prognosis of *Candida tropicalis* among non-*albicans* candidemia: a retrospective multicenter cohort study, Korea

Jae-Hoon Ko [a], Dong Sik Jung [b], Ji Yeon Lee [c], Hyun Ah Kim [c], Seong Yeol Ryu [c], Sook-In Jung [d], Eun-Jeong Joo [e], Shinhye Cheon [f], Yeon-Sook Kim [f], Shin-Woo Kim [g], Sun Young Cho [a], Cheol-In Kang [a], Doo Ryeon Chung [a], Nam Yong Lee [h], Kyong Ran Peck [a,*]

[a] Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[b] Division of Infectious Diseases, Dong-A University College of Medicine, Busan, Republic of Korea
[c] Division of Infectious Diseases, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea
[d] Division of Infectious Diseases, Chonnam National University Hospital, Gwangju, Republic of Korea
[e] Division of Infectious Diseases, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[f] Division of Infectious Diseases, Chungnam National University School of Medicine, Daejeon, Republic of Korea
[g] Division of Infectious Diseases, Kyungpook National University School of Medicine, Daegu, Republic of Korea
[h] Department of Laboratory Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

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ABSTRACT

To evaluate clinical features and prognostic factors of non-*albicans* candidemia, we conducted a retrospective multicenter cohort study at 7 university hospitals in Korea from January 2010 to February 2016. A total of 721 patients with non-*albicans* candidemia were included in the analysis. *C. tropicalis* was most commonly identified (36.5%), followed by *C. glabrata* (27.2%), *C. parapsilosis* (25.7%), and *C. krusei* (2.4%). Clinical presentation of *C. tropicalis* candidemia was most severe with highest median C-reactive protein level (10.1 mg/dL) and Acute Physiology and Chronic Health Evaluation II score (14, both $P \ll 0.05$). *C. tropicalis* showed the highest 14- and 30-day mortality (28.9% and 44.1%). In multivariate analysis, *C. tropicalis* infection was significantly related with 14- ($P = 0.005$) and 30-day mortality ($P = 0.033$). In conclusion, *C. tropicalis* infection presented most severely and showed worst clinical outcome among non-*albicans* candidemia.



## 1. Introduction

Non-*albicans Candida* infections are associated with antifungal resistance and poor outcome (Andes et al., 2012; Guinea et al., 2014). Overall proportions of non-*albicans* candidemia are increasing globally, while epidemiologic distribution of specific species varies with geographic regions (Andes et al., 2012; Guinea et al., 2014; Tan et al., 2016). Although a recent meta-analysis evaluated species-specific outcomes (Andes et al., 2012) and several studies from a Spanish cohort reported clinical aspect of non-*albicans* candidemia (Fernandez-Ruiz et al., 2014, 2015; Puig-Asensio et al., 2014, 2016), clinical studies of non-*albicans* candidemia with a sufficient number of patients are limited. Particularly, non-*albicans* candidemia in the Asia-Pacific region shows an increasing trend in association with increased antifungal use (Chapman et al., 2017; Guinea et al., 2014; Jung et al., 2012; Tan et al., 2016), and the proportion of non-*albicans* candidemia in Korea has exceeded that of *C. albicans* since 2006 (Jang et al., 2013; Jung et al., 2010, 2012; Won et al., 2015). To evaluate clinical presentation and prognostic factors of non-*albicans* candidemia, we conducted a retrospective multicenter cohort study between 2010 and 2016 in Korea.

## 2. Material and methods

### 2.1. Study design and population

We reviewed electronic medical records of individuals diagnosed with non-*albicans* candidemia between January 2010 and February 2016 at 7 university hospitals in Korea: Samsung Medical Center, a 1950-bed tertiary care center in Seoul; Dong-A University Hospital, a 962-bed tertiary care center in Busan; Keimyung University Dongsan Medical Center, a 909-bed tertiary care center in Daegu; Chonnam National University Hospital, a 1085-bed tertiary care center in Gwangju; Kangbuk Samsung Hospital, a 700-bed tertiary care center in Seoul; Chungnam National University Hospital, a 1354-bed tertiary care center in Daejeon; and Kyungpook National University Hospital, a 900-bed tertiary care center in Daegu. Candidemia cases from January to February 2016 were counted together with cases from 2015.

* Corresponding author. Tel.: +82-2-3410-0322; fax: +82-2-3410-0064.
*E-mail address:* krpeck@skku.edu (K.R. Peck).

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The cohort included adult patients (age ≥ 16) with non-*albicans* candidemia treated with intravenous antifungal agents using standard doses for candidemia (Pappas et al., 2016); only the first candidemia episode for each patient was included. Patients with the following criteria were excluded: 1) treatment with primary antifungal agents for ≪48 h, 2) treatment with a combination regimen, and 3) candidemia resistant to primary antifungal agents. Patients were followed for 30 days from onset of candidemia. This study was approved by the institutional review board of each hospital.

### 2.2. Data collection

Data collected included demographics, risk factors for candidemia, focus of infection, underlying diseases, factors for infection severity, types of primary antifungal agents, removal of central venous catheter during intravenous antifungal treatment, blood culture results, and date of death. Comorbidity was calculated by Charlson's weighted index of comorbidity (WIC), and severity of candidemia was determined by Acute Physiology and Chronic Health Evaluation (APACHE) II score (Charlson et al., 1987; Knaus et al., 1985).

### 2.3. Definitions

An episode of candidemia was defined as systemic manifestations and a positive culture in 1 or more sets of blood cultures. Echinocandin agents included caspofungin, micafungin, and anidulafungin; amphotericin B agents included conventional amphotericin B and liposomal amphotericin. Rare *Candida* species were defined as non-*albicans Candida* except *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. krusei*. Infection focus of candidemia was determined clinically by attending physicians according to the clinical symptom and signs and culture results from clinical specimens other than blood. Diagnosis of catheter-related bloodstream infection (CRBSI) followed criteria suggested by the Infectious Diseases Society of America (Mermel et al., 2009). Leukocytosis was defined as white blood cell (WBC) count ≫12,000/mm$^3$ and neutropenia as absolute neutrophil count ≪500 cells/mm$^3$ or expectation to decrease below this level within 48 h (Freifeld et al., 2011).

### 2.4. Microbiological methods

Collected blood culture specimens were incubated for 5 days by the BacT/ALERT 3D system (bioMérieux Inc., Marcy l'Etoile, France). A VITEK II automated system (bioMérieux Inc.) with a standard identification card was used for identification of *Candida* species and antimicrobial susceptibility testing (Pfaller et al., 2007).

### 2.5. Statistical analysis

For comparison between non-*albicans Candida* species, the Kruskal–Wallis test was used for continuous variables and a $\chi^2$ test for categorical variables. The Kaplan–Meier method was used to calculate 30-day survival probability of each non-*albicans Candida* species. The Cox proportional hazard model was used to evaluate risk factors for mortality. All factors relevant to outcomes were evaluated by univariate analysis, and those with statistical significance were included in multivariate analysis along with class of primary antifungal agent. All $P$ values were two-tailed, and $P \ll 0.05$ was considered statistically significant. IBM SPSS Statistics version 20.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

## 3. Results

### 3.1. Baseline characteristics, clinical presentation, and outcome of non-albicans candidemia

A total of 721 patients with non-*albicans* candidemia were included in clinical analysis after exclusion of 51 patients. *C. tropicalis* was most commonly identified (36.5%), followed by *C. glabrata* (27.2%), *C. parapsilosis* (25.7%), and *C. krusei* (2.4%). Severity, mortality, and underlying comorbidity of non-*albicans* candidemia patients did not differ between years.

Baseline characteristics, clinical presentation, and outcome according to each species are shown in Table 1. Demographics, risk factors for candidemia, and focus of candidemia were not significantly different between species. Underlying renal disease was more frequently associated with infections due to *C. glabrata* and *C. tropicalis* than other species ($P \ll 0.001$). Patients with *C. glabrata* candidemia were most likely to have solid cancer ($P = 0.005$); patients with *C. krusei* candidemia were most likely to have hematologic malignancy ($P \ll 0.001$). Charlson's WIC was highest in *C. glabrata* candidemia ($P \ll 0.001$). Among severity factors, leukocytosis was most frequently observed in *C. glabrata* candidemia ($P = 0.004$), while C-reactive protein (CRP) was highest in *C. tropicalis* candidemia ($P = 0.002$). APACHE II scores were highest in *C. tropicalis* and *C. krusei* candidemia and lowest in candidemia caused by *C. parapsilosis* and rare *Candida* species ($P \ll 0.001$). Most patients with *C. parapsilosis* candidemia were primarily treated with azoles ($P \ll 0.001$), while most patients with *C. krusei* candidemia were treated with echinocandins ($P = 0.002$) or amphotericin B ($P \ll 0.001$). The median duration of candidemia was 6 days overall and was not statistically different between species.

### 3.2. Analysis of 14- and 30-day mortality

Overall 14- and 30-day mortality was 20.4% and 34.5%, respectively (Table 1). Patients with non-*albicans* candidemia showed significantly different 30-day survival probability according to each specific species (Fig. 1; $P \ll 0.001$, by log-rank test). *C. tropicalis* candidemia showed highest mortality, followed by *C. glabrata* candidemia ($P \ll 0.001$). Low mortality was observed in candidemia caused by *C. parapsilosis* and rare *Candida* species. Although the 14-day mortality of *C. krusei* candidemia was low, 30-day mortality was similar to overall mortality.

Univariate and multivariate analyses were performed for 14- and 30-day mortality of non-*albicans* candidemia (Table 2). *C. tropicalis* infection and APACHE II score were associated with 14-day mortality (both $P \ll 0.05$). *C. tropicalis* infection was also associated with 30-day mortality, in addition to underlying hematologic malignancy and APACHE II score (all $P \ll 0.05$). Type of primary antifungal agent was not associated with 14- or 30-day mortality in the entire cohort and subgroup analyses comparing echinocandins and amphotericin B.

### 3.3. Effects of primary antifungal agents according to severity of infection

To evaluate potential associations between primary antifungal agents and infection severity, we performed subgroup analysis according to APACHE II score (Table 3). Patients were divided into 4 quartiles of APACHE II score. Univariate and multivariate analyses were performed as with the total cohort. In these subgroup analyses, no increasing or decreasing trend of HRs of clinical factors including primary antifungal agents was observed. There was also no statistical difference when the severity group was divided into low- and high-score groups.

## 4. Discussion

The advent of echinocandins changed paradigm of the management of candidiasis, being supported by strong clinical evidences including randomized controlled trials (RCTs) and a meta-analysis (Andes et al.,

**Table 1**
Baseline characteristics, clinical presentation, and outcome of 721 patients with non-*albicans* candidemia.

| Factor | Total ($N = 721$) | *Non-albicans Candida* species | | | | |
|---|---|---|---|---|---|---|
| | | *C. parapsilosis* ($n = 185$) | *C. tropicalis*[a] ($n = 263$) | *C. glabrata*[a] ($n = 196$) | *C. krusei*[a] ($n = 17$) | Rare *Candida* species ($n = 60$) |
| **Demographics** | | | | | | |
| Age | 66 (56–75) | 67 (55–76) | 67 (57–75) | 68 (57–76) | 61 (47–69) | 60 (50–72) |
| Male | 416 (57.7%) | 114 (61.6%) | 155 (58.9%) | 106 (54.1%) | 7 (41.2%) | 34 (56.7%) |
| **Risk factor** | | | | | | |
| CVC | 506 (70.2%) | 123 (66.5%) | 189 (71.9%) | 141 (71.9%) | 15 (88.2%) | 38 (63.3%) |
| CVC removal | 374 (51.9%) | 113 (61.1%) | 127 (48.3%) | 89 (45.4%) | 10 (58.8%) | 35 (58.3%) |
| Antibiotics | 614 (85.2%) | 153 (82.7%) | 232 (88.2%) | 162 (82.7%) | 16 (94.1%) | 51 (85.0%) |
| Recent surgery | 213 (29.5%) | 55 (29.7%) | 71 (27.0%) | 69 (35.2%) | 4 (23.5%) | 14 (23.3%) |
| TPN | 390 (54.1%) | 105 (56.8%) | 139 (52.9%) | 106 (54.1%) | 7 (41.2%) | 33 (55.0%) |
| **Infection focus** | | | | | | |
| Primary candidemia | 185 (25.7%) | 38 (20.5%) | 77 (29.3%) | 48 (24.5%) | 7 (41.2%) | 15 (25.0%) |
| CRBSI | 313 (43.4%) | 105 (56.8%) | 101 (38.4%) | 65 (33.2%) | 6 (35.3%) | 36 (60.0%) |
| Intra-abdominal | 116 (16.1%) | 23 (12.4%) | 42 (16.0%) | 46 (23.5%) | 3 (17.6%) | 2 (3.3%) |
| Urinary tract | 74 (10.3%) | 11 (5.9%) | 29 (11.0%) | 30 (15.3%) | 1 (5.9%) | 3 (5.0%) |
| Other | 33 (4.6%) | 8 (4.3%) | 14 (5.3%) | 7 (3.6%) | 0 (0.0%) | 4 (6.7%) |
| **Underlying disease** | | | | | | |
| Diabetes mellitus | 210 (29.1%) | 59 (39.1%) | 71 (27.0%) | 64 (32.7%) | 4 (23.5%) | 12 (20.0%) |
| Cardiovascular | 149 (20.7%) | 31 (16.8%) | 64 (24.3%) | 43 (21.9%) | 3 (17.6%) | 8 (13.3%) |
| Pulmonary | 89 (12.3%) | 26 (14.1%) | 40 (15.2%) | 17 (8.7%) | 0 (0.0%) | 6 (10.0%) |
| Liver | 74 (10.3%) | 18 (9.7%) | 31 (11.8%) | 18 (9.2%) | 2 (11.8%) | 5 (8.3%) |
| Renal | 217 (30.1%) | 35 (18.9%) | 90 (34.2%) | 77 (39.3%) | 5 (29.4%) | 10 (16.7%) |
| Solid cancer | 262 (36.3%) | 60 (32.4%) | 85 (32.3%) | 93 (47.4%) | 4 (23.5%) | 30 (33.3%) |
| Hematologic malig. | 111 (15.4%) | 6 (3.2%) | 63 (24.0%) | 22 (11.2%) | 11 (64.7%) | 9 (15.0%) |
| Charlson's WIC | 3 (2–6) | 2 (1–5) | 3 (2–5) | 4 (2–6) | 2 (2–5) | 2 (1–6) |
| **Severity of infection** | | | | | | |
| WBC ($\times 10^3/mm^3$) | 8.1 (4.2–12.9) | 8.0 (5.3–11.5) | 7.5 (3.0–13.5) | 9.8 (5.4–15.6) | 0.3 (0.1–9.7) | 7.3 (2.9–10.1) |
| Leukocytosis | 213 (29.5%) | 43 (23.2%) | 75 (28.5%) | 78 (39.8%) | 4 (23.5%) | 13 (21.7%) |
| Neutropenia | 91 (12.6%) | 2 (1.1%) | 56 (21.3%) | 15 (7.7%) | 10 (58.8%) | 8 (13.3%) |
| CRP (mg/dL) | 8.6 (4.2–14.4) | 8.1 (3.4–12.1) | 10.1 (4.7–16.0) | 8.2 (5.2–15.4) | 7.1 (1.5–18.4) | 7.2 (3.0–13.1) |
| APACHE II | 16 (11–21) | 14 (10–19) | 17 (12–22) | 16 (12–22) | 17 (12.3–21.5) | 13 (9–20) |
| **Primary antifungals** | | | | | | |
| Azoles | 462 (64.1%) | 149 (80.5%) | 161 (61.2%) | 111 (56.6%) | 1 (5.9%) | 40 (66.7%) |
| Echinocandins | 122 (16.9%) | 18 (9.7%) | 50 (19.0%) | 44 (22.4%) | 5 (29.4%) | 5 (8.3%) |
| Amphotericin B | 137 (19.0%) | 18 (9.7%) | 52 (19.8%) | 41 (20.9%) | 11 (64.7%) | 15 (25.0%) |
| **Outcome** | | | | | | |
| Days to clear-up[b] | 6 (4–10) | 6 (4–11) | 6 (4–9) | 7 (4–11) | 5 (2–13) | 6 (3–8) |
| Candidemia ≥1 wk[b] | 312 (46.2%) | 83 (48.3%) | 103 (41.7%) | 92 (50.5%) | 7 (41.2%) | 27 (46.6%) |
| 14-day mortality | 137 (20.4%) | 23 (12.4%) | 76 (28.9%) | 40 (20.4%) | 2 (11.8%) | 6 (10.0%) |
| 30-day mortality | 249 (34.5%) | 40 (21.6%) | 116 (44.1%) | 72 (36.7%) | 6 (35.3%) | 15 (25.0%) |

Data are expressed as number (%) of patients or median (IQR).
Abbreviations: CVC = central venous catheter; TPN = total parenteral nutrition; CRBSI = catheter-related bloodstream infection; malig. = malignancy; WIC = weighted index of comorbidity; WBC, =white blood cell; CRP = C-reactive protein; APACHE = Acute Physiology and Chronic Health Evaluation.
[a] Statistically associated with high comorbidities.
[b] 45 patients lacking follow-up culture within 7 days were excluded.

2012; Pappas et al., 2016; Reboli et al., 2007). Paradoxically, consecutive clinical studies were not eagerly conducted following these strong evidences: Most of recent clinical studies were based on a Spanish prospective cohort (Fernandez-Ruiz et al., 2014, 2015; Guinea et al., 2014; Puig-Asensio et al., 2014, 2016), and other studies focused on a specific species (Tseng et al., 2017). However, changing epidemiology of candidemia has been reported globally, and non-*albicans Candida* species are increasing in the Asia-Pacific region (Guinea et al., 2014; Ko et al., 2019; Tan et al., 2016). Accordingly, we conducted the present multicenter cohort study to evaluate clinical aspects of non-albicans candidemia.

Of note, *C. tropicalis*, the most common non-*albicans Candida* species (36.5%), was the strongest poor prognostic factor for 14-day mortality (HR 1.727, 95% CI 1.181–2.526, $P = 0.005$) and also associated with 30-day mortality (HR 1.366, 95% CI 1.026–1.819, $P = 0.033$) in the present analysis. Underlying comorbidities which may be associated with acquisition or prognosis of candidemia, such as diabetes or malignancies, were not prominent in the *C. tropicalis* group, while severity score was high (Pappas, 2006). The association of *C. tropicalis* with poor outcome was not noticed in the previous Spanish cohort study, probably because of small proportion of *C. tropicalis* in that cohort ($n = 57$, 13.7% of non-*albicans Candida*) (Puig-Asensio et al., 2014). In addition to the previous meta-analysis (Andes et al., 2012), our study emphasizes importance of *C. tropicalis* as a poor prognostic factor. Although pathogenic features of *C. tropicalis* have been identified (Deorukhkar et al., 2014; Negri et al., 2012; Rodrigues et al., 2003), specific antifungal agents have not proved beneficial to survival of this often-fatal *Candida* infection (Andes et al., 2012; Fernandez-Ruiz et al., 2015). Considering its high 30-day mortality rate (44.1%), further studies of treatments for *C. tropicalis* infection such as combination antifungal therapy are needed.

Other non-*albicans Candida* species also exhibited species-specific features. *C. parapsilosis* candidemia showed lowest 30-day mortality (21.6%), although it was not statistically significant in the multivariate analysis. The low mortality of *C. parapsilosis* without statistical significance in multivariate analysis is a consistent finding with previous reports (Andes et al., 2012; Fernandez-Ruiz et al., 2014; Puig-Asensio et al., 2014). This finding may be associated with high proportion of CRBSI in *C. parapsilosis* candidemia, which was also related with low mortality. Although *C. glabrata* candidemia was associated with high comorbidities, 14- and 30-day mortality was similar with those of overall non-*albicans* candidemia. *C. krusei* was also associated with high comorbidity and high 30-day mortality, but the interpretation is limited due to small number of included cases.

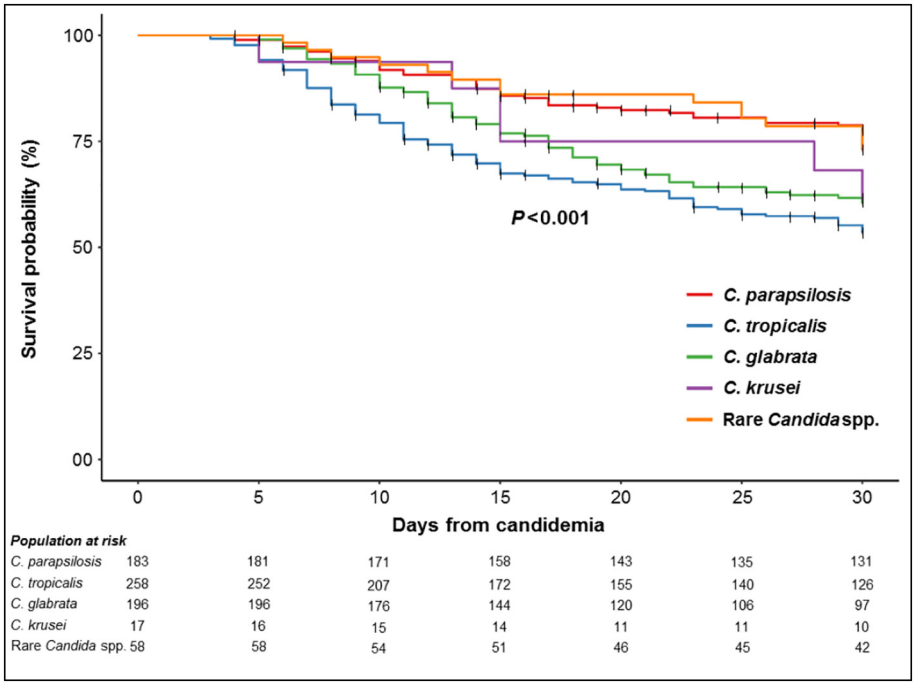


**Fig. 1.** Thirty-day survival probability for patients with non-*albicans* candidemia. Patients with non-*albicans* candidemia showed significantly different 30-day survival probability according to each specific species ($P \ll 0.001$, by log-rank test). *C. tropicalis* candidemia showed the highest 30-day mortality (44.1%), followed by *C. glabrata* (36.7%), *C. krusei* (35.3%), rare *Candida* species (25.0%), and *C. parapsilosis* (21.6%). *C. tropicalis* infections was a independent poor prognostic factor for 14- and 30-day mortality in the multivariate analysis (both $P \ll 0.05$).

Superiority of echinocandins over fluconazole for candidiasis treatment was demonstrated in an RCT, which showed better global success rates for anidulafungin than fluconazole, especially when treating *C. albicans* candidiasis (Reboli et al., 2007; Reboli et al., 2011). A *post hoc* analysis of this anidulafungin RCT suggested that anidulafungin was more effective for severely ill patients (Kett et al., 2011). Echinocandin use was also associated with improved survival of candidiasis in a meta-analysis of 7 RCTs (Andes et al., 2012). Meanwhile, our study as well as other individual RCTs and cohort studies (Eschenauer et al., 2013; Kuse et al., 2007; Lopez-Cortes et al., 2016; Mora-Duarte et al., 2002; Murri et al., 2016) did not show superiority of echinocandins over other antifungals. We also performed subgroup analysis, dividing patients into 4 severity groups according to APACHE II score, but echinocandins did not show superiority over fluconazole at any severity groups. A meta-analysis including both RCTs and cohort studies is required to resolve this controversial issue.

There are several limitations to the present study. Due to the observational nature of cohort design, infection severity and underlying

**Table 2**
Multivariate analyses for 14- and 30-day mortality of 721 patients with non-*albicans* candidemia.

| Outcome | Clinical factor | Multivariate analysis | |
|---|---|---|---|
| | | HR (95% CI) | *P* value |
| **14-day mortality** | CRBSI | 0.781 (0.542–1.126) | 0.186 |
| | Cardiovascular disease | 1.195 (0.808–1.768) | 1.195 |
| | Renal disease | 0.755 (0.494–1.155) | 0.755 |
| | Hematologic malignancy | 1.678 (0.986–2.857) | 0.057 |
| | Neutropenia | 0.884 (0.484–1.613) | 0.687 |
| | CRP level | 1.003 (0.983–1.023) | 0.787 |
| | APACHE II score | 1.068 (1.041–1.095) | ≪0.001 |
| | *C. parapsilosis* infection | 0.907 (0.527–1.563) | 0.726 |
| | *C. tropicalis* infection | 1.727 (1.181–2.526) | 0.005 |
| | Primary echinocandin treatment | 1.440 (0.910–2.277) | 0.119 |
| | Primary amphotericin B treatment | 1.421 (0.895–2.255) | 0.136 |
| **30-day mortality** | CRBSI | 0.880 (0.654–1.182) | 0.395 |
| | Intra-abdominal infection | 1.397 (0.981–1.990) | 0.064 |
| | Renal disease | 0.884 (0.646–1.209) | 0.441 |
| | Hematologic malignancy | 1.779 (1.153–2.744) | 0.009 |
| | Neutropenia | 0.882 (0.544–1.432) | 0.882 |
| | CRP level | 1.002 (0.988–1.017) | 0.750 |
| | APACHE II score | 1.066 (1.046–1.087) | ≪0.001 |
| | *C. parapsilosis* infection | 0.751 (0.504–1.120) | 0.160 |
| | *C. tropicalis* infection | 1.366 (1.026–1.819) | 0.033 |
| | Primary echinocandin treatment | 1.076 (0.753–1.538) | 0.688 |
| | Primary amphotericin B treatment | 1.218 (0.851–1.744) | 0.281 |

HR of each antifungal agent was relative to fluconazole (HR = 1).
Abbreviations: HR = hazard ratio; CI = confidence interval; CRBSI = catheter-related blood stream infection; CRP = C-reactive protein; APACHE = Acute Physiology and Chronic Health Evaluation.

**Table 3**
Evaluation of primary antifungal agents for 30-day mortality of non-*albicans* candidemia patients according to APACHE II score.

| Primary antifungal | APACHE II score | Multivariate analysis | |
|---|---|---|---|
| | | HR (95% CI) | *P* value |
| Echinocandins | 1st quartile ($1 \le$ score $\ll 11$, $n = 150$) | 0.816 (0.228–2.925) | 0.755 |
| | 2nd quartile ($11 \le$ score $\ll 16$, $n = 196$) | 1.523 (0.573–4.051) | 0.399 |
| | 3rd quartile ($16 \le$ score $\ll 21$, $n = 182$) | 0.686 (0.325–1.449) | 0.323 |
| | 4th quartile ($21 \le$ score $\ll 41$, $n = 193$) | 1.090 (0.682–1.743) | 0.718 |
| | Low score ($1 \le$ score $\ll 16$, $n = 346$) | 1.070 (0.503–2.275) | 0.861 |
| | High score ($16 \le$ score $\ll 41$, $n = 375$) | 0.937 (0.623–1.409) | 0.755 |
| Amphotericin B | 1st quartile ($1 \le$ score $\ll 11$, $n = 150$) | 1.207 (0.443–3.295) | 0.713 |
| | 2nd quartile ($11 \le$ score $\ll 16$, $n = 196$) | 1.556 (0.683–3.548) | 0.293 |
| | 3rd quartile ($16 \le$ score $\ll 21$, $n = 182$) | 1.475 (0.784–2.778) | 0.228 |
| | 4th quartile ($21 \le$ score $\ll 41$, $n = 193$) | 0.744 (0.423–1.308) | 0.304 |
| | Low score ($1 \le$ score $\ll 16$, $n = 346$) | 1.261 (0.676–2.352) | 0.466 |
| | High score ($16 \le$ score $\ll 41$, $n = 375$) | 0.985 (0.646–1.504) | 0.946 |

HR of each antifungal agent was relative to fluconazole (HR = 1).
Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; HR = hazard ratio; CI = confidence interval.

comorbidities were different between treatment groups. We performed multivariate analysis to adjust for potential confounding factors, and 14-day and 30-day mortality analyses showed coherent results. Although primary use of echinocandin increased dramatically midway through our study period, mortality, severity, and comorbidity of candida infection remained constant. Since the population of this study was limited to non-*albicans* candidemia, the results cannot be applied to *C. albicans* which still took the majority of candidemia as a single species during the study period. Lastly, to evaluate the effects of specific antifungal agents, we excluded 7 candidemia cases resistant to primary antifungal agents. Since the antifungal susceptibility criteria are applied in species-specific manner, features of antifungal resistant candidemia need to be evaluated separately (CLSI, 2017; Ko et al., 2018).

## 5. Conclusions

In a retrospective multicenter cohort study of non-*albicans* candidemia patients, *C. tropicalis* infection presented most severely and showed worst outcome, while patients with *C. glabrata* candidemia had higher comorbidity. Type of primary antifungal agents was not associated with outcomes of non-*albicans* candidemia.

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## Conflicts of interest

None of the authors have any conflicts of interest to report.

## References

Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis 2012;54:1110–22.
Chapman B, Slavin M, Marriott D, Halliday C, Kidd S, Arthur I, et al. Changing epidemiology of candidaemia in Australia. J Antimicrob Chemother 2017;72:1103–8.
Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
Clinical and Laboratory Standards Institute (CLSI). *Performance standards for antifungal susceptibility testing of yeasts.* 1st ed. CLSI supplement M60. Wayne, PA. Clinical and Laboratory Standards Institute 2017.
Deorukhkar SC, Saini S, Mathew S. Virulence factors contributing to pathogenicity of Candida tropicalis and its antifungal susceptibility profile. Int J Microbiol 2014;2014,456878.
Eschenauer GA, Carver PL, Lin SW, Klinker KP, Chen YC, Potoski BA, et al. Fluconazole versus an echinocandin for Candida glabrata fungaemia: a retrospective cohort study. J Antimicrob Chemother 2013;68:922–6.
Fernandez-Ruiz M, Aguado JM, Almirante B, Lora-Pablos D, Padilla B, Puig-Asensio M, et al. Initial use of echinocandins does not negatively influence outcome in Candida parapsilosis bloodstream infection: a propensity score analysis. Clin Infect Dis 2014;58:1413–21.
Fernandez-Ruiz M, Puig-Asensio M, Guinea J, Almirante B, Padilla B, Almela M, et al. Candida tropicalis bloodstream infection: incidence, risk factors and outcome in a population-based surveillance. J Infect 2015;71:385–94.
Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56–93.
Guinea J, Zaragoza O, Escribano P, Martin-Mazuelos E, Peman J, Sanchez-Reus F, et al. Molecular identification and antifungal susceptibility of yeast isolates causing fungemia collected in a population-based study in Spain in 2010 and 2011. Antimicrob Agents Chemother 2014;58:1529–37.
Jang MJ, Shin JH, Lee WG, Kim MN, Lee K, Lee HS, et al. In vitro fluconazole and voriconazole susceptibilities of Candida bloodstream isolates in Korea: use of the CLSI and EUCAST epidemiological cutoff values. Ann Lab Med 2013;33:167–73.
Jung SI, Shin JH, Song JH, Peck KR, Lee K, Kim MN, et al. Multicenter surveillance of species distribution and antifungal susceptibilities of Candida bloodstream isolates in South Korea. Med Mycol 2010;48:669–74.
Jung SI, Shin JH, Choi HJ, Ju MY, Kim SH, Lee WG, et al. Antifungal susceptibility to amphotericin B, fluconazole, voriconazole, and flucytosine in Candida bloodstream isolates from 15 tertiary hospitals in Korea. Ann Lab Med 2012;32:426–8.
Kett DH, Shorr AF, Reboli AC, Reisman AL, Biswas P, Schlamm HT. Anidulafungin compared with fluconazole in severely ill patients with candidemia and other forms of invasive candidiasis: support for the 2009 IDSA treatment guidelines for candidiasis. Crit Care 2011;15:R253.
Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
Ko JH, Peck KR, Jung DS, Lee JY, Kim HA, Ryu SY, et al. Impact of high MIC of fluconazole on outcomes of Candida glabrata bloodstream infection: a retrospective multicenter cohort study. Diagn Microbiol Infect Dis 2018;92:127–32.
Ko JH, Jung DS, Lee JY, Kim HA, Ryu SY, Jung SI, et al. Changing epidemiology of non-albicans candidemia in Korea. J Infect Chemother 2019;25:388–91.
Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 2007;369:1519–27.
Lopez-Cortes LE, Almirante B, Cuenca-Estrella M, Garnacho-Montero J, Padilla B, Puig-Asensio M, et al. Empirical and targeted therapy of candidemia with fluconazole versus echinocandins: a propensity score-derived analysis of a population-based, multicentre prospective cohort. Clin Microbiol Infect 2016;22:733 e1–8.
Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49:1–45.
Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347:2020–9.
Murri R, Scoppettuolo G, Ventura G, Fabbiani M, Giovannenze F, Taccari F, et al. Initial antifungal strategy does not correlate with mortality in patients with candidemia. Eur J Clin Microbiol Infect Dis 2016;35:187–93.
Negri M, Silva S, Henriques M, Oliveira R. Insights into Candida tropicalis nosocomial infections and virulence factors. Eur J Clin Microbiol Infect Dis 2012;31:1399–412.
Pappas PG. Invasive candidiasis. Infect Dis Clin North Am 2006;20:485–506.
Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1–50.

Pfaller MA, Diekema DJ, Procop GW, Rinaldi MG. Multicenter comparison of the VITEK 2 yeast susceptibility test with the CLSI broth microdilution reference method for testing fluconazole against Candida spp. J Clin Microbiol 2007;45:796–802.

Puig-Asensio M, Padilla B, Garnacho-Montero J, Zaragoza O, Aguado JM, Zaragoza R, et al. Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain. Clin Microbiol Infect 2014;20:O245–54.

Puig-Asensio M, Fernandez-Ruiz M, Aguado JM, Merino P, Lora-Pablos D, Guinea J, et al. Propensity score analysis of the role of initial antifungal therapy in the outcome of Candida glabrata bloodstream infections. Antimicrob Agents Chemother 2016;60:3291–300.

Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356:2472–82.

Reboli AC, Shorr AF, Rotstein C, Pappas PG, Kett DH, Schlamm HT, et al. Anidulafungin compared with fluconazole for treatment of candidemia and other forms of invasive candidiasis caused by Candida albicans: a multivariate analysis of factors associated with improved outcome. BMC Infect Dis 2011;11:261.

Rodrigues AG, Pina-Vaz C, Costa-de-Oliveira S, Tavares C. Expression of plasma coagulase among pathogenic Candida species. J Clin Microbiol 2003;41:5792–3.

Tan TY, Hsu LY, Alejandria MM, Chaiwarith R, Chinniah T, Chayakulkeeree M, et al. Antifungal susceptibility of invasive Candida bloodstream isolates from the Asia-Pacific region. Med Mycol 2016;54:471–7.

Tseng TY, Chen TC, Ho CM, Lin PC, Chou CH, Tsai CT, et al. Clinical features, antifungal susceptibility, and outcome of Candida guilliermondii fungemia: an experience in a tertiary hospital in mid-Taiwan. J Microbiol Immunol Infect 2018;51:552–8.

Won EJ, Shin JH, Choi MJ, Lee WG, Park YJ, Uh Y, et al. Antifungal susceptibilities of bloodstream isolates of Candida species from nine hospitals in Korea: application of new antifungal breakpoints and relationship to antifungal usage. PLoS One 2015;10, e0118770.