

# Analysis of the distribution and antifungal susceptibility of *Candida albicans* and non-*albicans Candida* isolated from human blood culture

Jae-Sik Jeon, Jae Kyung Kim

Department of Biomedical Laboratory Science, Dankook University College of Health Sciences, Cheonan, South Korea

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## RESEARCH

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Please cite this paper as: Jeon JS, Kim JK. Analysis of the distribution and antifungal susceptibility of *Candida albicans* and non-*albicans Candida* isolated from human blood culture. AMJ 2019;12(3):90–97.

<https://doi.org/10.21767/AMJ.2018.3572>

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### Corresponding Author:

Jae Kyung Kim

Department of Biomedical Laboratory Science  
Dankook University College of Health Sciences  
119, Dandae-ro, Dongnam-gu, Cheonan-si, Chungnam  
31116, South Korea

Email: [nerowolf2@dankook.ac.kr](mailto:nerowolf2@dankook.ac.kr)

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## ABSTRACT

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### Background

Candidaemia is a growing concern worldwide, and its species distribution has shifted toward non-*albicans Candida* in recent decades, especially in patients with malignancy. The population continues to age worldwide, especially in developing countries and among groups with high socioeconomic status.

### Aims

This study aimed to analyse the *Candida* species and associated antifungal susceptibility in one region of Korea.

### Methods

From December 2014 to June 2018, 126 specimens of *Candida* species from blood cultures were analysed using various methods. We used VITEK 2 to perform the blood culture and the R statistical program for analysis. In addition, an antifungal susceptibility test was performed.

### Results

*C. albicans* was detected in 51 (40.5 per cent), *C. glabrata* and *C. tropicalis* in 24 (19.0 per cent), and *C. parapsilosis* in 16 (12.7 per cent) specimens. The mean age of patients with *C. albicans* was 63.8 years and that of patients with non-*albicans Candida* was 65.6 years. We performed an antifungal susceptibility test using six agents, and eight (6.3 per cent) specimens exhibited antifungal resistance. The data showed that *C. albicans* was the most commonly detected species. Moreover, a large proportion of the elderly subjects were infected with *C. albicans*, and the rate of antifungal agent resistance was as high as 6.3 per cent.

### Conclusion

Our study indicates that *C. albicans* was the most commonly detected species and the infection rate was high among elderly patients. Therefore, clinics should remain vigilant, and preparedness levels must be increased in regions with a high percentage of elderly people.

### Key Words

Age group, candidiasis, frequency, VITEK 2

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### What this study adds:

#### 1. What is known about this subject?

*Candida albicans* can cause serious infections in immunocompromised individuals and increased mortality has been reported with delays in the initiation of appropriate antifungal therapy.

#### 2. What new information is offered in this study?

In Korea, the infection rate in elderly people (average 63.8–65.6 years) was high and the antifungal drug resistance was 6.3 per cent.

#### 3. What are the implications for research, policy, or practice?

In order to lower the mortality rate, the monitoring of *Candida* antifungal agent resistance in elderly populations should be strengthened.

## Background

Globally, *Candida albicans* is the most frequently (50 per cent–70 per cent) reported causative agent of candidaemia.<sup>1,2</sup> *Candida albicans* and emerging non-*albicans Candida* species (NACs) such as *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* can cause superficial infections of the oral and vaginal mucosa as well as disseminated bloodstream and deep tissue infections.<sup>3</sup>

*C. albicans* is typically harmless to healthy individuals, but it can cause serious infections in immunocompromised individuals or in those who received long-term, broad-spectrum antibiotic therapy.<sup>4,5</sup> *Candida* species are among the four most common isolates in nosocomial bloodstream infections.<sup>6,7</sup> Sepsis caused by *Candida* species has higher mortality than that due to bacterial pathogens, reaching 53.7 per cent–63.5 per cent in *Candida*-associated septic shock.<sup>7,8</sup> Candidiasis is an infectious disease with high morbidity and mortality. The prevalence of candidiasis has dramatically increased in the past 20 years, and the gradual increase in resistance of those NACs to antifungal agents makes clinical treatment difficult.<sup>9</sup>

Increased mortality has been reported in candidaemia patients with delays in the initiation of appropriate antifungal therapy.<sup>2,10</sup> It is very important to understand the mechanisms of antifungal agent resistance to improve the efficiency of treatment, since *Candida* infections have a high impact on immunocompromised patients.<sup>11</sup> Early detection of organism susceptibility to antibiotic agents has to be carried out for the successful treatment of any infectious disease.<sup>11,12</sup>

Hence, this study aimed to analyse the detected microorganisms and their antimicrobial resistance in a tertiary care centre in Cheonan, Korea.

## Method

### Samples

In this study, the clinical data were obtained from cases that were referred to Dankook University Hospital between December 2014 and June 2018 in which *Candida* species were detected by blood culture and antifungal resistance (AFR) was detected using VITEK 2. The data were collected retrospectively, and we analysed the results using these data. A total of 126 blood culture specimens were collected consecutively during this period, and the participants were enrolled in the study. The study protocol was approved by the Institutional Review Board (IRB) of Dankook University and retrospectively registered (IRB Approval No: 2018-09-

002). The study was conducted in conformance with the tenets of the Declaration of Helsinki.

### Culturing and antimicrobial resistance evaluation

Various tests were performed with subcultures grown for 24 to 55h on Sabouraud dextrose agar at 35°C. Each single colony was suspended in 5mL sterile distilled water and vortexed. The turbidity at a wavelength of 530nm was adjusted to a McFarland standard of 0.5 with sterile distilled water. This suspension was used for the broth microdilution method, after appropriate dilution according to the standardised protocol. Inoculum suspensions for use with the VITEK 2 ID-YST cards (bioMérieux, Durham, NC, USA) were obtained from the same overnight cultures, with the turbidity adjusted to 1.8–2.2 McFarland standard using the bioMérieux Densichek instrument, according to the manufacturer's recommendations.

Specimens were directly inoculated into the VITEK 2 susceptibility testing device using AST-YS07 cards (bioMérieux). The antifungal susceptibility test results were available for amphotericin B (AB), caspofungin (CAS), fluconazole (FLU), flucytosine (FCT), micafungin (MCF), and voriconazole (VRC). Minimum inhibitory concentration (MIC) values were used to categorise isolates as susceptible (S), intermediate (I), or resistant (R), based on routine diagnostics with VITEK 2 following the manufacturer's guidelines. Specimens were inoculated even if their values were lower than the standard McFarland turbidity of 1.8–2.2.

### Data analysis

Data were analysed using the R statistical program (version 3.3.3, Comprehensive R Archive Network; <https://www.r-project.org>) and are presented as medians and ranges. The chi-square test was used to analyse categorical data.

## Results

A total of 126 specimens were analysed, of which 79 were obtained from men and 47 were obtained from women; the ratio between the sexes was 1.68:1. The entire sample set was classified into nine types of *Candida*, with 51 *C. albicans* (40.5 per cent) and 75 NACs (59.5 per cent). Among them, the number of specimens with *C. glabrata* and *C. tropicalis* was the highest (24, 19.0 per cent), followed by *C. parapsilosis* (16, 12.7 per cent). The mean age of the patients was 64.9 years (range, new born–94.4 years); male patients were aged 65.0 years, and female patients were aged 64.8 years (Table 1). Only the top three species are listed in the table; the remaining species are combined into "Other" owing to the small number of detected species.

The mean age of the *C. albicans* group was 63.8 years and that of the NAC group was 65.6 years (Table 2). *C. albicans* was most commonly found in patients aged 60–69 years, while NACs were most commonly identified in patients aged 70–79 years (Figure 1A). AFR was mostly observed among patients aged 60–69 years (Figure 1B).

The distribution by period was analysed on a monthly average basis. The results showed that *C. albicans* was most frequently detected during summer, and the AFR specimens and highest AFR rate were detected during spring (Figure 2A). On the contrary, NACs were most frequently detected during fall, and the AFR specimens and highest AFR rate were detected during summer (Figure 2B) (Table 3).

Antifungal susceptibility tests were performed using six agents (AB, CAS, FLU, FCT, MCF, and VRC). Eight (6.3 per cent) specimens exhibited AFR. One specimen showed resistance to AB, FLU, and VRC (data not shown). AFR was frequently detected in *C. albicans* treated with VRC and in NACs treated with FLU (2, 2.7 per cent).

## Discussion

*Candida* species are one of the major causes of nosocomial bloodstream infections worldwide. Despite the availability of an expanded antifungal armamentarium, the mortality associated with invasive *Candida* infections remains high, ranging between 19 per cent and 49 per cent.<sup>13</sup> This study provides an analysis of the distribution and antifungal susceptibility of 126 isolates of *Candida* species according to patient age group, period, and type of agent to which the fungi developed resistance.

We detected nine types of *Candida* species. *C. albicans* was the most commonly detected species, followed by *C. glabrata* and *C. tropicalis*. This finding is similar to those reported in previous studies. Jabeen et al. reported that *C. albicans* (27.9 per cent) was the most commonly detected species in Pakistan in 2016, followed by *C. parapsilosis* (26.9 per cent) and *C. tropicalis* (26.0 per cent).<sup>2</sup> Guinea reported that *C. albicans* (56.0 per cent) was the most commonly detected species in Iceland in 2013,<sup>14</sup> followed by *C. glabrata* (16.0 per cent) and *C. tropicalis* (13.0 per cent).<sup>15</sup> Orasch et al. reported that *C. albicans* (61.9 per cent) was the most common species in Switzerland followed by *C. glabrata* (17.5 per cent) and *C. tropicalis* (5.9 per cent).<sup>16</sup> Although the rankings and proportions were slightly different, *C. albicans* was found to be the most commonly detected species in all of these studies.

*Candida* species were commonly detected in patients aged

50–79 years (69.8 per cent), and the mean patient age was 65.6 years. *Candida* was mainly found in older patients. Schmid et al. reported that *Candida* species were commonly detected in patients aged 55 years.<sup>17</sup> Loster et al. reported that they were commonly detected among those aged 65.7 years.<sup>18</sup> Several other studies reported that they were commonly detected among patients aged between 50 and 79 years.<sup>19-21</sup> In our study, the mean age was found to increase with year, but it was not considered significant ( $p=0.1294$ ).

*C. albicans* was more commonly detected in summer, followed by spring. AFR *C. albicans* was more commonly detected in spring. NACs were commonly detected in fall, followed by summer, and AFR NACs were commonly detected in summer. The rates of detection might be related to temperature, but the correlation was not statistically significant. However, additional research is needed to confirm this.

In this study, 8 of 126 (6.3 per cent) specimens were detected as AFR strains. These results were similar to those of previous studies. The proportion of AFR strains in Peru was reported to be 2.6 per cent;<sup>22</sup> that in Brazil was 5.2 per cent;<sup>23</sup> and that in China was 8.8 per cent.<sup>24</sup> We presumed that the region and climate have an impact on antifungal susceptibility. However, additional confirmatory research is needed.

## Conclusion

In conclusion, *C. albicans* was the most commonly detected species. In addition, a large proportion of elderly people were infected with *C. albicans*, and the rate of AFR reached approximately 6.3 per cent. Therefore, clinics should exercise vigilance, and preparedness must be increased in societies with a high percentage of elderly individuals. This study has some limitations. It was conducted only in one region of Korea and included a small number of participants because of the short observation period. Due to the retrospective nature of this study, additional data could not be obtained. However, the data in this study can be used as a basis for studying the antibiotic resistance of *Candida* species detected in blood cultures.

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### **PEER REVIEW**

Not commissioned. Externally peer reviewed.

### **CONFLICTS OF INTEREST**

The authors declare that they have no competing interests.

### **FUNDING**

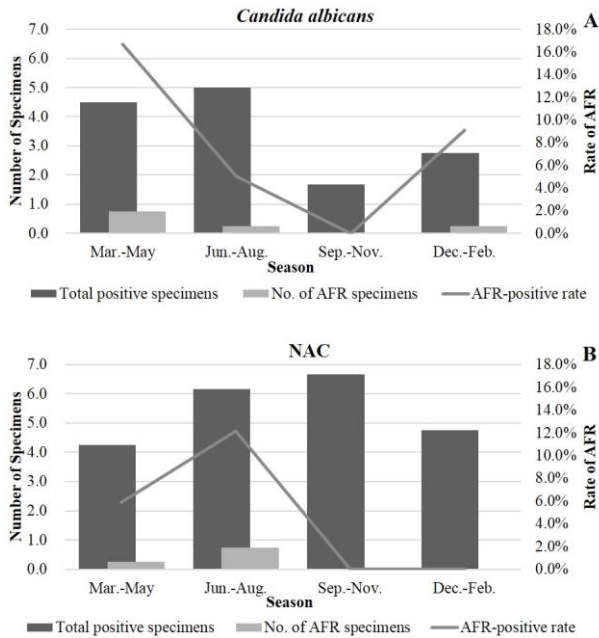
None

### **ETHICS COMMITTEE APPROVAL**

The study protocol was approved by the Institutional Review Board (IRB) of Dankook University and retrospectively registered (IRB Approval No: 2018-09-002). The study was conducted in conformance with the tenets of the Declaration of Helsinki.

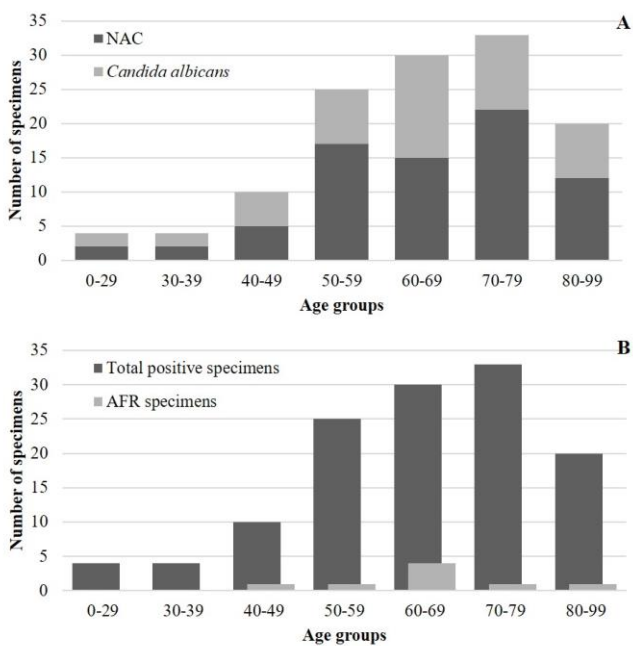
**Figure 1: Number of *Candida albicans* and NAC specimens with/without AFR by age group.**

**A: The ratio of *C. albicans* and NACs by age group. B: The total detected *Candida* specimens and AFR specimens by age group**



**Figure 2: Number of *Candida albicans* and NAC specimens with/without AFR by season.**

**A: The ratio of *C. albicans* and AFR *C. albicans* specimens by season. B: The ratio of NAC and AFR NAC specimens by season**



**Table 1: Analysis of specimens based on the number and age group**

	Number (%)	No. of AFR specimens (%)	Average age
Total specimens	126 (100.0)	8 (6.3)	64.9
Male	79 (62.7)	5 (6.3)	65.0
Female	47 (37.3)	3 (6.4)	64.8
<i>Candida albicans</i>	51 (40.5)	5 (9.8)	63.8
Non- <i>albicans Candida</i>	75 (59.5)	3 (4.0)	65.6
<i>Candida glabrata</i>	24 (19.0)	2 (8.3)	63.0
<i>Candida tropicalis</i>	24 (19.0)	0 (0.0)	68.4
<i>Candida parapsilosis</i>	16 (12.7)	0 (0.0)	65.5
Other	11 (8.7)	1 (9.1)	65.6

AFR; antifungal resistance



**Table 2: Distribution of age group and *Candida* type**

Resistance	Total no. of specimens	Antifungal Drugs																	
		Amphotericin B			Caspofungin <sup>SDD</sup>			Fluconazole <sup>SDD</sup>			Flucytosine			Micafungin <sup>SDD</sup>			Voriconazole <sup>SDD</sup>		
		S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
<i>Candida albicans</i>	51	48	1	2	51	0	0	49	1	1	51	0	0	51	0	0	47	0	4
Non- <i>albicans</i>	75	74	1	0	75	0	0	72	1	2	75	0	0	75	0	0	74	0	1
<i>Candida glabrata</i>	24	24	0	0	24	0	0	22	1	1	24	0	0	24	0	0	23	0	1
<i>Candida tropicalis</i>	24	24	0	0	24	0	0	24	0	0	24	0	0	24	0	0	24	0	0
<i>Candida parapsilosis</i>	16	16	0	0	16	0	0	16	0	0	16	0	0	16	0	0	16	0	0
Other	11	10	1	0	11	0	0	10	0	1	11	0	0	11	0	0	11	0	0

SDD; Susceptible-dose dependent, S; Sensitive, I; Intermediate, R; Resistant

**Table 3: MIC range of antifungal drugs**

Antifungal Drugs	MIC range ( $\mu\text{g/mL}$ )
Amphotericin B	0.25-16
Caspofungin <sup>SDD</sup>	0.25-4
Fluconazole <sup>SDD</sup>	1-64
Flucytosine	1-64
Micafungin <sup>SDD</sup>	0.06-4
Voriconazole <sup>SDD</sup>	0.12-8

SDD; Susceptible-dose dependent, MIC; minimum inhibitory concentration