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

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**RESEARCH**

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**ABSTRACT**

**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 analyze 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 analyzed 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

**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.2,3 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.5

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.4,5 Candida species are among the four most common isolates in nosocomial bloodstream infections.6,7 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.7,8 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.9

Increased mortality has been reported in candidaemia patients with delays in the initiation of appropriate antifungal therapy.2,10 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.11 Early detection of organism susceptibility to antibiotic agents has to be carried out for the successful treatment of any infectious disease.11,12

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 (2.7 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.\(^1\) 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).\(^2\) Guinea reported that *C. albicans* (56.0 per cent) was the most commonly detected species in Iceland in 2013,\(^3\) followed by *C. glabrata* (16.0 per cent) and *C. tropicalis* (13.0 per cent).\(^4\) 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).\(^5\) 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.\(^6\) Loster et al. reported that they were commonly detected among those aged 65.7 years.\(^7\) Several other studies reported that they were commonly detected among patients aged between 50 and 79 years.\(^8\)\(^9\) 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,\(^10\) that in Brazil was 5.2 per cent,\(^11\) and that in China was 8.8 per cent.\(^12\) 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.

**References**

1. Farooqi JQ, Jabeen K, Saeed N, et al. Invasive candidiasis in Pakistan: clinical characteristics, species distribution and antifungal susceptibility. J Med Microbiol. 2013;62:259–268. https://doi.org/10.1099/jmm.0.048785-0.
2. Jabeen K, Kumar H, Farooqi J, et al. Agreement of direct
antifungal susceptibility testing from positive blood culture bottles with the conventional method for Candida species. J Clin Microbiol. 2016;54:343–348. https://doi.org/10.1128/JCM.02432-15.

3. Whaley SG, Berkow EL, Rybak JM, et al. Azole antifungal resistance in Candida albicans and emerging non-albicans Candida species. Front Microbiol. 2017;7:2173. https://doi.org/10.3389/fmicb.2016.02173.

4. Brown GD, Denning DW, Gow NA, et al. Hidden killers: human fungal infections. Sci Transl Med. 2012;4:165rv13. https://doi.org/10.1126/scitranslmed.3004404.

5. Liang W, Guan G, Dai Y, et al. Lactic acid bacteria differentially regulate filamentation in two heritable cell types of the human fungal pathogen Candida albicans. Mol Microbiol. 2016;102:506–519. https://doi.org/10.1111/mmi.13475.

6. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004;39:309–317. https://doi.org/10.1086/421946.

7. Idelevich EA, Grunevald CM, Wüllenweber J, et al. Rapid identification and susceptibility testing of Candida species from positive blood cultures by combination of direct MALDI-TOF mass spectrometry and direct inoculation of Vitek 2. PLoS One. 2014;9:e114834. https://doi.org/10.1126/scitranslmed.3004404.

8. Bassetti M, Righi E, Ansaldi F, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. Intensive Care Med. 2014;40:839–845. https://doi.org/10.1007/s00134-014-3310-z.

9. Kim GY, Jeon JS, Kim JK. Isolation frequency characteristics of Candida species from clinical specimens. Mycobiology, 2016;44:99–104. https://doi.org/10.5941/MYCO.2016.44.2.99.

10. Taur Y, Cohen N, Dubnow S, et al. Effect of antifungal therapy timing on mortality in cancer patients with candidemia. Antimicrob Agents Chemother. 2010;54:184–190. https://doi.org/10.1128/AAC.00945-09.

11. Zaidi KU, Mani A, Parmar R, et al. Antifungal susceptibility pattern of Candida albicans in human infections. Open Biological Sci J. 2018;4:1–6. https://doi.org/10.2174/2352633501804010001.

12. Hospenthal DR, Murray CK, Rinaldi MG. The role of antifungal susceptibility testing in the therapy of candidiasis. Diagn Microbiol Infect Dis. 2004;48:153–160. https://doi.org/10.1016/j.diagmicrobio.2003.10.003.

13. Mokaddas EM, Al-Sweih NA, Khan ZU. Species distribution and antifungal susceptibility of Candida bloodstream isolates in Kuwait: a 10-year study. J Med Microbiol. 2007;56:255–259. https://doi.org/10.1099/jmm.0.46817-0.

14. Guinea J. Global trends in the distribution of Candida species causing candidemia. Clin Microbiol Infect. 2014;20:5–10. https://doi.org/10.1111/1469-0691.12539.

15. Asmundsdottir LR, Erlendsdottir H, Gottfredsson M. Nationwide study of candidemia, antifungal use, and antifungal drug resistance in Iceland, 2000 to 2011. J Clin Microbiol. 2013;51:841–848. https://doi.org/10.1128/JCM.02566-12.

16. Orasch C, Marchetti O, Garbino J, et al. Candida species distribution and antifungal susceptibility testing according to European Committee on Antimicrobial Susceptibility Testing and new vs. old Clinical and Laboratory Standards Institute clinical breakpoints: a 6-year prospective candidaemia survey from the fungal infection network of Switzerland. Clin Microbiol Infect. 2014;20:698–705. https://doi.org/10.1111/1469-0691.12440.

17. Schmid J, Tortorano AM, Jones G, et al. Increased mortality in young candidemia patients associated with presence of a Candida albicans general-purpose genotype. J Clin Microbiol. 2011;49:3250–3256. https://doi.org/10.1128/JCM.00941-11.

18. Loster JE, Wieczorek A, Loster BW. Correlation between age and gender in Candida species infections of complete denture wearers: a retrospective analysis. Clin Interv Aging. 2016;11:1707–1714. https://doi.org/10.2147/CIA.S116658.

19. Leung WK, Dassanayake RS, Yau JY, et al. Oral colonization, phenotypic, and genotypic profiles of Candida species in irradiated, dentate, xerostomic nasopharyngeal carcinoma survivors. J Clin Microbiol. 2000;38:2219–2226.

20. Dias IJ, Trajano ERIS, Castro RD, et al. Antifungal activity of linalool in cases of Candida spp. isolated from individuals with oral candidiasis. Braz J Biol. 2018;78:368–374. https://doi.org/10.1590/1519-6984.171054.

21. Wu PF, Liu WL, Hsieh MH, et al. Epidemiology and antifungal susceptibility of candidemia isolates of non-albicans Candida species from cancer patients. Emerg Microbes Infect. 2017;6:e87. https://doi.org/10.1038/emi.2017.74.

22. Rodriguez L, Bustamante B, Huaroto L, et al. A multicentric study of Candida bloodstream infection in Lima-Callao, Peru: species distribution, antifungal resistance
and clinical outcomes. PLoS One, 2017;12:e0175172. https://doi.org/10.1371/journal.pone.0175172.

23. Goulart LS, Santiago EF, Ramon JL, et al. Species distribution and antifungal susceptibility to vulvovaginal Candida spp. in southern Mato Grosso State, Brazil. J Bras Patol Med Lab. 2016;52:233–237. https://doi.org/10.5935/1676-2444.20160039.

24. Xiao M, Sun ZY, Kang M, et al. Five-year national surveillance of invasive candidiasis: species distribution and azole susceptibility from the China Hospital Invasive Fungal Surveillance Net (CHIF-NET) study. J Clin Microbiol. 2018;56:e00577–18. https://doi.org/10.1128/JCM.00577-18.

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CONFLICTS OF INTEREST
The authors declare that they have no competing interests.

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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.

| No. of AFR specimens (% | Average age |
|-------------------------|------------|
| 8 (6.3)                 | 64.9       |
| 5 (6.3)                 | 65.0       |
| 3 (6.4)                 | 64.8       |
| 5 (9.8)                 | 63.8       |
| 3 (4.0)                 | 65.6       |
| 2 (8.3)                 | 63.0       |
| 0 (0.0)                 | 68.4       |
| 0 (0.0)                 | 65.5       |
| 1 (9.1)                 | 65.6       |

AFR; antifungal resistance

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

| Number (%) | No. of AFR specimens (%) | Average age |
|------------|--------------------------|------------|
| 126 (100.0)| 8 (6.3)                  | 64.9       |
| 79 (62.7)  | 5 (6.3)                  | 65.0       |
| 47 (37.3)  | 3 (6.4)                  | 64.8       |
| 51 (40.5)  | 5 (9.8)                  | 63.8       |
| 75 (59.5)  | 3 (4.0)                  | 65.6       |
| 24 (19.0)  | 2 (8.3)                  | 63.0       |
| 24 (19.0)  | 0 (0.0)                  | 68.4       |
| 16 (12.7)  | 0 (0.0)                  | 65.5       |
| 11 (8.7)   | 1 (9.1)                  | 65.6       |

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 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 |
| Candida albicans | 51                     | 48 | 1 | 2 | 51 | 0 | 0 | 49 | 1 | 1 | 51 | 0 | 0 | 51 | 0 | 0 | 47 | 0 | 4 |
| Non-albicans     | 75                     | 74 | 1 | 0 | 75 | 0 | 0 | 72 | 1 | 2 | 75 | 0 | 0 | 75 | 0 | 0 | 74 | 0 | 1 |
| Candida glabrata | 24                     | 24 | 0 | 0 | 24 | 0 | 0 | 22 | 1 | 1 | 24 | 0 | 0 | 24 | 0 | 0 | 23 | 0 | 1 |
| Candida tropicalis | 24                  | 24 | 0 | 0 | 24 | 0 | 0 | 24 | 0 | 0 | 24 | 0 | 0 | 24 | 0 | 0 | 24 | 0 | 0 |
| Candida parapsilosis | 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 (μg/mL) |
|------------------|-------------------|
| Amphotericin B   | 0.25-16           |
| Caspofungin SDD  | 0.25-4            |
| Fluconazole SDD  | 1-64              |
| Flucytosine      | 1-64              |
| Micafungin SDD   | 0.06-4            |
| Voriconazole SDD | 0.12-8            |

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