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Research Article

Isolation Frequency Characteristics of *Candida* Species from Clinical Specimens

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Abstract *Candida* spp. is an invasive infectious fungus, a major risk factor that can increase morbidity and mortality in hospitalized patients. In this study, 2,508 *Candida* spp. were isolated from various clinical specimens collected from university hospitals from July 2011 to October 2014. They were identified in order to determine isolation frequencies and characteristics by specimen, gender, age group, year, season, and month. The strain-specific isolation rate of *Candida* spp. is in the order of *Candida albicans* (1,218 strains, 48.56%), *Candida glabrata* (416 strains, 16.59%), *Candida utilis* (305 strains, 12.16%), *Candida tropicalis* (304 strains, 12.12%), and *Candida parapsilosis* (116 strains, 4.63%) and these five species accounted for more than 94% of the total strains. Of the specimens, *Candida* spp. were most frequently isolated from urine-catheter, followed by urine-voided, blood, sputum, other, open pus, vaginal discharge, Tip, ear discharge, bronchial aspiration and bile, in that order. Looking at the age distribution, the detection rate of patients in their 60s and older was significantly higher at 75.8% (1,900/2,508). The detection rate of patients in their 20s and younger was shown to be very low at 2.55% (64/2,508). By year, the detection rate of non-*albicans Candida* spp. showed a tendency to gradually increase each year compared with *C. albicans*. As isolation of *Candida* spp. from clinical samples at the specie level can vary depending on characteristics of the patient, sample, season, etc., continual studies are required.

Keywords *Candida albicans*, *Candida glabrata*, *Candida* spp., Non-*albicans Candida* spp.

Fungal infections by opportunistic pathogens such as *Candida*, *Cryptococcus*, and *Aspergillus* and the resulting morality in patients with a lowered immune system are showing a steady upward trend in the world [1]. In the United States, based on the analysis of death certificate data from 1980 to 1997, the number of deaths due to fungal infections has increased by 3.4 times from 1,577 to 6,577 people [2]. *Candida* spp. are the most common causative organism of fungal infections. In the United States, candidemia accounts for about 8% of pathogenic bloodstream infections, and *Candida* spp. are the 4th most common causative organism of nosocomial bloodstream infection, which is one of the major risk factors that increase morbidity and mortality in hospitalized patients [3-5]. In the past, the most causative pathogen was *Candida albicans*, but recently various types of *Candida* spp. such as *Candida parapsilosis*, *Candida glabrata*, and *Candida krusei* have emerged as important opportunistically infectious fungi [6, 7]. Candidiasis is an infectious disease with high morbidity and mortality, of which prevalence has dramatically increased in the past 20 years [8, 9], and the gradual increase in the resistance of those non-*albicans Candida* spp. to antifungal agents makes clinical treatment difficult. In this study, using VITEK-2 (AS-TS01; bioMérieux, Hazelwood, MO, USA), an automated analytical equipment in Dankook University Hospital located in Cheonan, Chungnam, *Candida* spp. were identified during the last three years and by determining the isolation frequency and characteristics by specimen, gender, age, year, month, and season, we intended to help basic research on candidiasis and clinical treatment of *Candida* infection.

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MATERIALS AND METHODS

Clinical specimens. The subjects of this study were 2,508 strains (1,005 patients) of *Candida* spp. which were isolated from the clinical specimens collected at the Dankook

University Hospital for three years from July 2011 until October 2014. For suspicious infection potentially occurring nosocomially and out of the hospital, samples including sputum, bronchial wash solution, blood, pus, urine, and feces were cultured on blood agar for fungal identification. This study was approved by the Institutional Review Board Deliberations Exemption of Dankook University (IRB No. DKU 2015-10-010).

Identification of *Candida* spp. The test organisms evaluated in this study included 3 American Type Culture Collection (ATCC) strains that have been established as QC strains for species identification tests: *C. albicans* ATCC 10231, *C. tropicalis* ATCC 200956, *C. glabrata* ATCC 90030 by Clinical and Laboratory Standards Institute (CLSI, 2008) [10] For the study, all strains were isolated from clinical samples. Tests were performed from subcultures grown for 24 to 55 hr on Sabouraud dextrose agar at 35°C. Each single colony was suspended in 5 mL of sterile distilled water and vortexed. The turbidity at a wavelength of 530 nm was adjusted to a McFarland standard of 0.5 with sterile distilled water. This suspension (approximately 1×10^6 to 5×10^6 CFU/mL) was used for the broth microdilution method, after appropriate dilution according to the standardized protocol. Inoculum suspensions for use with the VITEK 2 ID-YST cards were obtained from the same overnight cultures, with the turbidity being adjusted to a 1.8 to 2.2 McFarland standard using the bioMerieux Densicheck instrument, according to the manufacturer's recommendations.

The isolated *Candida* spp. were identified using VITEK 2 ID-YST (bioMérieux, Durham, NC, USA), an automated analytical equipment. VITEK 2 system and ID-YST card. The VITEK ID-YST card consists of 64 wells with 47 fluorescent biochemical tests. They comprise 20 carbohydrate and six organic acid assimilation tests. The integrated VITEK 2 instrument automatically filled, sealed and transferred the cards into an incubator (incubation temperature was 35°C). Every 15 min the cards were automatically subjected to a fluorescence measurement. Each profile was interpreted according to a specific algorithm. After an incubation period of 15 hr, the profile result was compared to the ID-YST database, which led to the final identification of the microorganism [11]. The identification of the strains was performed using internal transcribed spacer (ITS) sequencing as a reference method [12]. In accordance with the classification method by International Commission of the taxonomy of Fungi (http://www.fungaltaxonomy.org/).

RESULTS

Identification of *Candida* spp. The total number of isolated *Candida* spp. was 2,508 strains, in which *C. albicans* (48.6%) was isolated the most frequently, followed

Table 1. Distribution of *Candida* spp. in different clinical specimens

Specimens	*Candida* species						Total
	C. albicans	*C. glabrata*	*C. utilis*	*C. tropicalis*	*C. parapsilosis*	Other	
Urine, cath	450 (35.6)	262 (20.7)	276 (21.8)	192 (15.2)	34 (2.7)	51 (4.0)	1,265 (100.0)
Urine, voided	131 (43.7)	66 (22.0)	19 (6.3)	44 (14.7)	5 (1.7)	35 (11.7)	300 (100.0)
Blood	133 (50.4)	54 (20.5)	6 (2.3)	22 (8.3)	29 (11.0)	20 (7.6)	264 (100.0)
Sputum	215 (98.6)	0 (0.0)	0 (0.0)	3 (1.4)	0 (0.0)	0 (0.0)	218 (100.0)
Other	83 (50.6)	21 (12.8)	2 (1.2)	26 (15.9)	15 (9.1)	17 (10.4)	164 (100.0)
Open pus	52 (70.3)	2 (2.7)	0 (0.0)	5 (6.8)	12 (16.2)	3 (4.1)	74 (100.0)
Vaginal discharge	56 (98.2)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	57 (100.0)
Tip	31 (56.4)	2 (3.6)	2 (3.6)	8 (14.5)	7 (12.7)	5 (9.1)	55 (100.0)
Ear discharge	4 (13.8)	3 (10.3)	0 (0.0)	1 (3.4)	8 (27.6)	13 (44.8)	29 (100.0)
Bronchial aspiration	18 (94.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	19 (100.0)
Bile	12 (70.6)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	17 (100.0)
Ascites (peritoneal)	6 (54.5)	1 (9.1)	0 (0.0)	2 (18.2)	2 (18.2)	0 (0.0)	11 (100.0)
Bronchoalveolar lavage	8 (72.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (27.3)	0 (0.0)	11 (100.0)
Closed pus	4 (66.7)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	6 (100.0)
Pleural fluid	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	4 (100.0)
Transtracheal aspiration	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)
Peritoneal fluide	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	3 (100.0)
Perianal discharge	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
Prostate secretion	1 (50.0)	1 (50)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
Perineal discharge	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Throat swab	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Urethral discharge	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Total	1,218 (48.6)	416 (16.6)	305 (12.2)	304 (12.1)	116 (4.6)	149 (5.9)	2,508 (100.0)

Values are presented as number (%).
BAL, bronchoalveolar lavage.

by *C. glabrata* (16.6%), *Candida utilis* (12.2%), *C. tropicalis* (12.1%), and *C. parapsilosis* (4.6%) in that order. These five strains accounted for more than 94% of the total strains isolated. Consistency between the result above and of sequencing was confirmed by ITS in random samples conducted for quality control (Table 1).

Distribution of *Candida* spp. by specimen. Looking into the isolation rate of each strain of *Candida* spp., which were isolated from a variety of clinical specimens, of a total of 2,508 strains, *C. albicans* 50.5% (1,162/2,302), *C. glabrata* 18.1% (416/2,303), *C. utilis* 13.2% (305/2,303), *C. tropicalis* 13,2% (304/2,303), and *C. parapsilosis* 5% (116/2,303) were isolated, in that order (Table 1). In particular, *C. albicans* was isolated most frequently from urine catheter, followed by sputum, blood, urine-voided and other in that order, *C. glabrata* was isolated most frequently from urine catheter, followed by urine-voided, blood and other in that order, and *C. utilis* was detected most frequently from urine catheter, followed by urine-voided, blood and other in that order. In addition, *C. tropicalis* was isolated most frequently from urine catheter, followed by urine-voided, other and blood and sputum in that order and *C. parapsilosis* was isolated most frequently from urine catheter, followed by blood, other, open pus and urine-voided in that order. Notable points are that *C. glabrata*, *C. utilis*, and *C. parapsilosis* were not detected from sputum and that *C. albicans* was isolated from every specimen, even though there were significant differences between each specimen.

Distribution of *Candida* spp. by gender and age. Urine catheter was the specimen from which *Candida* spp. were most prominently isolated, both in women and men, followed by urine-voided, blood, sputum, other, open pus, vaginal discharge, Tip, ear discharge, bronchial aspiration and bile in that order. In particular, the isolation rates from urine catheter and blood were slightly higher in men and those from urine-voided, sputum and other were slightly higher in women. Combining entire specimens, the sex ratio of males and females was 1 : 1.1 (1,197 : 1,311), and was slightly higher in women (Fig. 1).

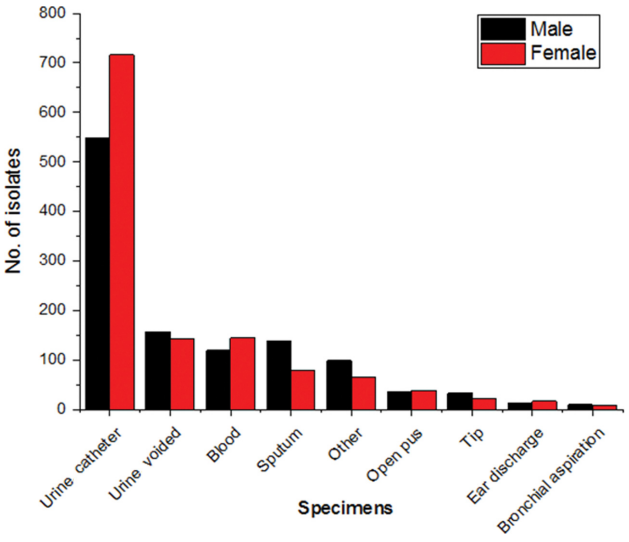

Fig. 1. *Candida* spp. found in specimens of males and females.

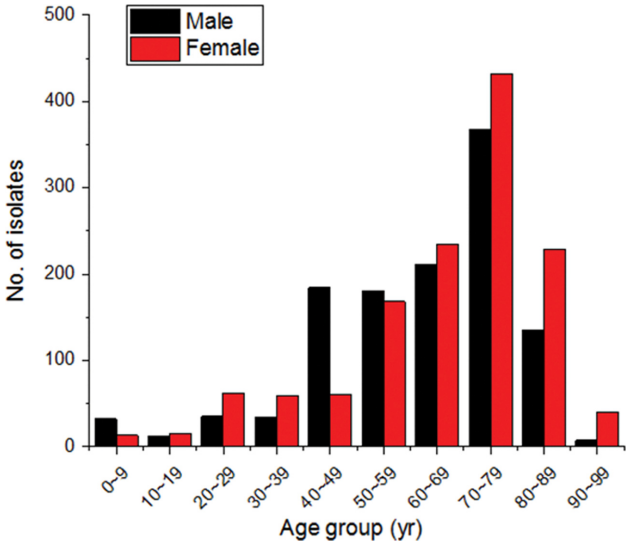

Fig. 2. *Candida* spp. analysis in different age groups.

Meanwhile, the age distribution of isolated *Candida* spp. showed that the isolation rate of the patients in their 60s and older was significantly higher at 75.8% (1,900/2,508), of which the isolation rate of the patients in their 80s, in particular, was highest at 48.2% (1,209/2,508). For patients in their 50s, men were infected by 119 strains and women were infected by 52 strains, showing that the isolation rate of men was more than twice higher than that of women. Patients in their 20s and younger showed a low isolation rate at 2.55% (64/2,508), of which the isolation rate of the patients in their 20s, in particular, was the lowest at 0.76% (19/2,508) among the all age groups (Fig. 2).

The composition ratios of *Candida albicans* and non-*albicans Candida* spp. by year. The composition ratios of *Candida albicans* and non-*albicans Candida* spp. were analyzed and the results showed that the isolation rate in 2011 was 51.9% and 48.1%, respectively, in 2012, 51.7% and 48.3%, respectively, in 2013, 47.3% and 52.7%, respectively and in 2014, 45.4% and 54.6%, respectively. This indicates that there is a tendency for the detection rate of *C. albicans* to become gradually reduced each year, whereas the detection rate of non-*albicans Candida* spp. gradually increases (Fig. 3).

Distribution of *Candida* spp. by year. Looking into the distribution of the isolated *Candida* spp. by year, in 2011, *C. albicans* was most frequently isolated at 51.92% (135/260), followed by *C. glabrata* at 26.15% (68/260) and *C. tropicalis* at 14.23% (37/260); in 2012, *C. albicans* was

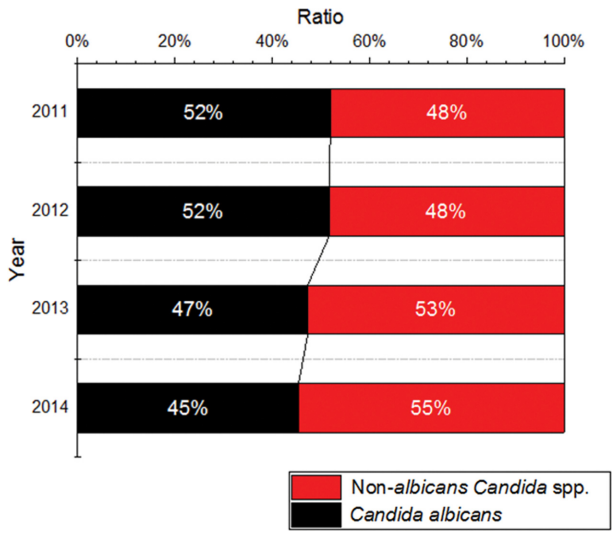

Fig. 3. Ratio of *Candida albicans* and non-*albicans Candida* spp. according to year.

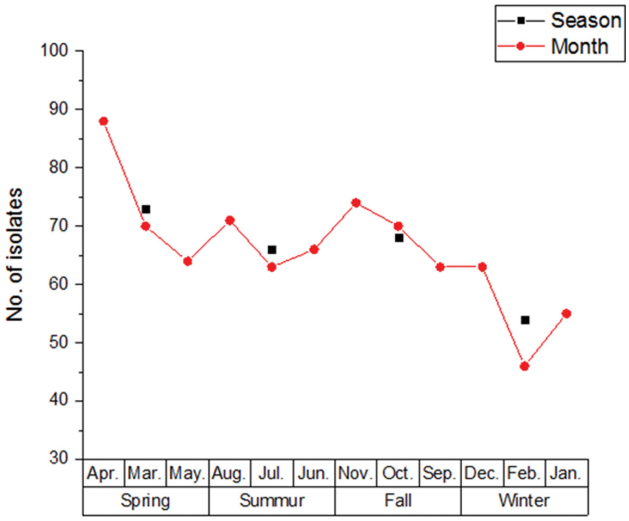

Fig. 4. *Candida* spp. number isolated in different months.

most frequently isolated at 51.65% (344/666), followed by *C. glabrata* at 18.77% (125/666) and *C. tropicalis* at 16.37% (109/666); in 2014, *C. albicans* was most frequently isolated at 45.42% (233/513), followed by *C. glabrata* at 20.66% (106/513) and *C. tropicalis* at 9.75% (50/513), showing a trend of similar isolation rates between strains each year. However, in 2013 it showed a very different pattern, in which *C. albicans* was most frequently isolated at 47.33% (506/1,069), followed by *C. utilis* at 24.70% (264/1,069) and *C. glabrata* at 10.94% (117/1,069) in that order. On the other hand, in 2011 and 2012, the isolation rate of *C. albicans* accounted for more than 50%, but in 2013 and 2014, it gradually began to decrease (Table 2).

The distribution of *Candida* spp. by season and month. Looking into the seasonal distribution of *Candida* spp., which were isolated from 2011 to 2014, they were isolated most frequently in spring (73 strains) and autumn (68 strains) in that order, and then in the winter the rate was the lowest with 54 strains isolated. Also, *Candida* spp. were most frequently isolated in April (88 strains) and November (74 strains), in that order; the smallest number of strains were isolated on February (46 strains) (Fig. 4).

DISCUSSION

There are about 100 *Candida* spp., of which *C. albicans* is the most frequently detected opportunistic pathogen. The

Table 2. Analysis of *Candida* spp. by years according to specimens

Specimens	2011		2012		2013		2014	
	Samples	Ratio (%)	Samples	Ratio (%)	Samples	Ratio (%)	Samples	Ratio (%)
C. albicans	135	51.92	344	51.65	506	47.33	233	45.42
C. glabrata	68	26.15	125	18.77	117	10.94	106	20.66
C. utilis	0	0.00	16	2.40	264	24.70	25	4.87
C. tropicalis	37	14.23	109	16.37	108	10.10	50	9.75
C. parapsilosis	8	3.08	30	4.50	34	3.18	44	8.58
Candida spp., non *albicans*	6	2.31	15	2.25	21	1.96	24	4.68
C. famata	1	0.38	12	1.80	6	0.56	7	1.36
C. lusitaniae	1	0.38	6	0.90	3	0.28	10	1.95
C. haemulonii	1	0.38	1	0.15	5	0.47	4	0.78
C. krusei	2	0.77	2	0.30	0	0.00	4	0.78
C. sphaerica	0	0.00	0	0.00	3	0.28	3	0.58
C. lipolytica	0	0.00	4	0.60	1	0.09	0	0.00
C. intermedia	0	0.00	1	0.15	0	0.00	2	0.39
C. rugosa	1	0.38	0	0.00	0	0.00	0	0.00
C. norvegensis	0	0.00	1	0.15	0	0.00	0	0.00
C. guilliermondii	0	0.00	0	0.00	1	0.09	0	0.00
C. kefyr	0	0.00	0	0.00	0	0.00	1	0.19
Total	260	100.00	666	100.00	1069	100.00	513	100.00

detection rate of non-*albicans Candida* species (*C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. lusitaniae*, and *C. glabrata*), excluding *C. albicans,* has gradually increased [8, 13-16] and the case fatality rate caused by these invasive mycoses is as high as 22.4% [5].

A total of 2,508 strains of *Candida* spp. were isolated in this study, of which the aforementioned five strains accounted for over 94% of the total strains isolated. Compared with the results of other researchers, it was also found that the detection rate of *C. albicans* was highest and the aforementioned five strains accounted for over 95%, which was consistent with the findings in this study [17]. Looking at each specimen type, *C. albicans* was the most frequently detected in urine, which showed a nearly similar pattern with other studies conducted at home and abroad but with some differences [18, 19]. In particular, the vast majority of *Candida* spp. was detected from urine catheter, which showed a great difference when voiding and thus, it is thought that these fungal infections mostly resulted from nosocomial infection which was mediated through catheters. The study of Shin *et al.* [17] showed that the isolation rate of *Candida* spp. was 30.1% in sputum, 25.0% in random-urine, 15.8% in blood and 13.5% in urine catheter, which showed some slight differences in the detection rates from urine catheter, urine-voided, blood, and sputum obtained in the study. On the other hand, a domestic study reported that *C. albicans* (40.8%), *C. parapsilosis* (17.3%), *C. tropicalis* (16.5%), and *C. glabrata* (6.3%) were frequently isolated from blood, in that order [20], and the results of Uh *et al.*'s experiment [21] showed that the order was as follows: *C. albicans* (43.8%), *C. parapsilosis* (20.8%), *C. glabrata* (13.8%), and *C. tropicalis* (9.2%) [21]. These slight differences in the isolation rate are believed to have been resulted from the effect of seasonal, locational, environmental differences of the fungi which belong to genus *Candida*. The isolation rates of these fungi by specimen/gender were examined and the sex ratio of males and females was 1 : 1.1 (1,197 : 1,311) with no significant difference in both sexes. The results of other studies also showed a similar results with the present study regarding some strains and sex ratio [17]. This study showed that the infection rate by *Candida* spp. had a tendency to increase with increasing age, whereas other researchers reported that the number of patients 20~49 years old, especially patients 30~39 years old had the highest rate of infection [19]. On the other hand, it reported that the detection rate of teenagers, in particular, was the lowest [17, 22], which showed nearly identical results with this study. It is thought that the infection rate of teenagers is relatively low because this age group of teenagers has a vigorous immune system and participation in outdoor activities is low.

Meanwhile, the isolation rate of *Candida* spp. was highest on average in April and lowest in February, which was consistent with the results of Shin *et al.* [17], However, it was the isolation rate of *Candida* spp. being highest in the summer [17, 22, 23] was somewhat different from the reports. Fungal infections by *Candida* occur easily in a body with a weakened immune system, which is caused by opportunistic pathogens. Based on this fact, it is thought that the immune system is significantly weakened at the change of seasons such as spring and fall, leading to a susceptible condition of infection. Winter susceptibility to these fungi is greatly lowered by reduced activity due to the decrease in temperatures. In the past, infections were mainly caused by *C. albicans*, but recently, infectious diseases caused by *C. tropicalis* and *C. parapsilosis* are also increasing [24, 25]. Although *C. albicans* was most frequently detected in this study, the detection ratio of *C. albicans* over the entire *Candida* spp. has been declining year by year.

The reasons for the increased isolation rate of 16 *Candida* species other than *C. albicans* can be attributed to be the incremental factors related to the advancement of automated test equipment in hospitals as well as the increase in the opportunistic pathogens of different species according to the environmental changes and weakened immune functions in the human body. On the other hand, this study showed that the overall detection rate of *C. albicans* was decreased, but given that it is still an important microbial species accounting for more than 50% of the entire detection rate, it requires continuous monitoring and support of additional clinical studies.

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