ART & TECHNOLOGY PUBLISHING PTE. LTD.

Progress in Applied Microbiology

2022 Volume 3, Issue 1

ISSN: 2630-4791

Frequency of *Candida* Strains Isolated from Candidiasis Patients at A Tertiary Hospital over the Last 10 Years

Yu-Yean Hwang[1], On-Kyun Kang[1], Chang-Eun Park[2], Sung-No Hong[3], Young-Kwon Kim[4], Hee-Jae Huh[5], Nam-Yong Lee[5]

[1]Department of Laboratory Medicine, Samsung Medical Center, Seoul, Republic of Korea

[2]Department of Biomedical Laboratory Science, Molecular Diagnostics Research Institute, Namseoul University, Cheonan, Republic of Korea

[3]Department of Clinical Laboratory Science, Dongnam Health University, Suwon, Republic of Korea

[4]Department of Health Sciences, The Graduate School of Konyang University, Daejeon, Republic of Korea

[5]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Corresponding author: Young-Kwon Kim, ykkim3245@konyang.ac.kr

Abstract

Candidemia is a major cause of nosocomial infections resulting in increased morbidity and mortality. It remains a serious risk in inpatients and increases medical treatment costs. From 2009 to 2018, *Candida* strains (3,533) isolated from blood culture tests at the S Hospital were analyzed according to the period, year, sex, age, ward, etc. During the entire period, 54,739 of 717,996 blood culture tests showed a positive rate (7.6%) and the *Candida* isolation rate was 3,533 (6.4%) out of the positive blood culture tests. Among the *Candida* isolates, *C. albicans* was the most common (33.8%), followed by *C. tropicalis* (28.6%), *C. glabrata* (19.8%), *C. parapsilosis* (7.8%), and *C. krusei* (4.0%). In early (2009–2013) or late (2014–2018) isolation, *C. tropicalis* decreased by 3.8% and *C. glabrata* increased by 3.4%. The isolation frequency became higher in patients aged above 50, *C. parapsilosis* (31.3%) in age 1–10, *C. tropicalis* (30.3%) and *C. glabrata* (27.6%) in age 41–50, and *C. tropicalis* (28.6%) in age > 80 are relatively frequent. Most species had been isolated from males, except for *C. krusei*, which was isolated in a relatively high proportion from females (60.9%). Therefore, a systematic and continuous nosocomial infection control system should be established for appropriate treatment as per antifungal treatment guidelines. The system should continuously monitor the distribution of *Candida* species and provide rapid identification results.

Keywords

Blood culture
Candidemia
Candida bloodstream infections
Candida species
Non-*albicans Candida* species

1. Introduction

Bloodstream infections (BSIs) caused by microorganisms, including bacteria, fungi, viruses, and parasites, frequently lead to sepsis and septic shock in patients requiring admission to intensive care units (ICUs) [1,2]. BSI represents a global public health concern. Studies from European and North American countries estimate that BSI causes over 2 million cases and 250,000 fatalities each year, with a mortality rate ranging from 13% to 30% [3]. *Candida*-related candidemia and invasive candidiasis are among the leading causes of BSI, posing significant risks to hospitalized patients and increasing healthcare expenses as the major causes of morbidity and mortality [4]. *Candida* species (spp.) are responsible for over 90% of all fungal BSIs [5]. In the United States, BSIs caused by *Candida* spp. are ranked fourth, while in Europe, it is ranked seventh. It is also the third leading cause of late-onset sepsis in neonates [6]. *Candida* species are commonly isolated from patients who have been hospitalized due to fungal bloodstream infections [7]. Hospital-based studies have indicated that the global incidence of *Candida* BSI ranges between 0.3% and 5% per 1,000 hospitalized patients [8]. In Korea, the occurrence rate varies depending on the geographic location and time of investigations, with a recent study having reported that bloodstream infections caused by fungi accounted for 6.8% [9]. In ICU settings, patients infected with *Candida* spp. in the bloodstream have elevated mortality rates and longer hospital stays than those infected with Gram-positive and Gram-negative bacteria [10]. Despite significant therapeutic efforts, candidemia still bears approximately 60% overall mortality rate [11].

Among fungi, *Candida albicans* has been the leading causative agent of BSI for a considerable time [12]. Nonetheless, non-*albicans Candida* species, including *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*, have become increasingly prevalent and are causing infections more frequently [13]. In a study conducted by Diekema *et al.* [14], which compared the four-year period before and after the introduction of echinocandins and fluconazole, it was observed that the proportion of *C. albicans* bloodstream infection decreased marginally from 61% to 60%. However, after the commencement of echinocandins and fluconazole administration, *C. albicans* incidence further decreased. Another study examining the usage of echinocandins and fluconazole found that the prevalence of *C. parapsilosis* and *C. glabrata* rose from 0% to 16%, indicating that extensive use of antifungal agents played a role in the change of the distribution of *Candida* species in BSI [15]. This is consistent with the aforementioned study. The causative agents of invasive candidiasis, including candidemia, are various species of *Candida*. The distribution and susceptibility to antimicrobials of *Candida* species should be considered. Variations in antifungal resistance rates can differ among institutions, regions, and countries, and these disparities have been linked to factors such as previous exposure to azole agents, artificial implants, cancer surgery, total parenteral nutrition (TPN), bacterial sepsis, female gender, leukocytosis, and immunosuppressive drugs [16]. They are believed to stem from differences in antifungal usage and infection control policies across hospitals and regions. Hence, epidemiological investigations of bloodstream infections caused by fungi, coupled with routine evaluations of species distribution and susceptibility to antimicrobials, are indispensable for devising suitable diagnostic and therapeutic strategies. Such probes are significant not only in comprehending the epidemiology of fungal infections but also in establishing treatment policies regarding suspected fungal infections. The aim of this study was to examine the incidence of fungal species isolation in blood cultures to obtain relevant data that can be used for diagnosis, prognosis, and treatment of patients suffering from bacteremia caused by fungi.

2. Materials and methods

2.1. Study subjects

This retrospective study focuses on clinical strains, isolated through blood culture from patients referred for diagnosis of bloodstream infections at Samsung Medical Centre. The tertiary care hospital, located in Seoul, South Korea has a capacity of 1,979 beds. The data from this study covers a 10-year period from January 2009 to December 2018, and was obtained using electronic medical record (EMR) results after fungal identification and antimicrobial susceptibility testing as part of routine patient care. This study was conducted under an exemption from review (SMC 2019-07-74).

2.2. Research methods

(1) Blood culture

The BACT/ALERT 3D system (bioMerieux, Marcy l'Etoile, France) was used to culture a total of 717,996 specimens from inpatients and outpatients with clinically suspected bacteremia. 6–10 mL of blood were drawn, with 3–10 mL respectively being placed into aerobic (bioMerieux Plus Aerobic/F medium) and anaerobic (bioMerieux Plus Anaerobic/F medium or bioMerieux Peds Plus/F medium) culture bottles. The bottles were then incubated at a temperature ranging from 35°C to 37°C to ascertain the levels of CO_2 produced by the microorganisms present within the BACT/ALERT 3D system. The quantity of CO_2 produced by the microorganisms during their growth is assessed every 10 minutes by the LED sensor system, which illuminates and measures the color change from blue to yellow when positive, and kept incubated for 5 days until the determination of a positive result. The blood culture bottles that tested positive were Gram-stained and subcultured by extracting a portion of the culture fluid, appropriately streaking on blood agar plates (BAP) (SHINYANG Diagnostics, Seoul, Korea), MacConkey agar (KORMED, Seongnam, Korea), chocolate agar (KORMED), and brucella agar (KORMED) using aseptic techniques. Subsequently, the plates were incubated in a 35°C CO_2 incubator for 18–24 hours (Thermo Fisher Scientific, Massachusetts, USA). Brucella agar was incubated in an anaerobic chamber (BACTRON, Sheldon Manufacturing Inc, OR, USA) for 48 hours.

(2) Fungal identification

Fungal identification was carried out using the VITEK 2 system YST ID card (bioMerieux, Marcy l'Etoile, France) from 2009 to 2015. The broth was prepared in 0.45% sterile saline with a turbidity (McFarland) of 1.8–2.2. Then, the YST card was inserted into the olivine tube in the smart carrier system (scs), patient information was entered, and the cassette was lifted and loaded into the VITEK 2. The results were read the next day. Standard strains of *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were utilized as sensitivity controls for every test, according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. VITEK MS (bioMerieux, Marcy l'Etoile, France) was employed from 2016 until 2018, with VITEK MS-DS target slides prepared and calibrated utilizing *Escherichia coli* ATCC 8739, located at a centered QC spot. Sterile 1 μL loops were used to harvest colonies of 18–24 hour-old bacteria, which were then applied as a thin layer to the center of a spot on an MS-DS slide. 0.5 μL VITEK® MS-FA (formic acid) was added to the spot via pipette, and the FA was allowed to evaporate for 1–3 minutes to increase efficiency of extraction. Subsequently, 1 μL of VITEK® MS-CHCA (α-cyano-4-hydroxycinnamic acid)

matrix was pipetted onto the center of the spot, and the MS-DS slide spot was left to air dry. After 5 minutes, the MS-DS slide was checked for any "crystal formation" that may have formed a yellowish film. The VITEK® MS instrument was used to examine the prepared sample slide. After the slide was loaded into the equipment, it was then placed under high vacuum conditions. The sample underwent ionization by a laser beam and the resulting protein "cloud" was emitted. The proteins were then accelerated using an electric charge and the time of flight of both light and heavy proteins was recorded. After being detected by a sensor, the protein components of each sample were spectroscopically analyzed. The resulting spectra were compared with a thoroughly analyzed database of *Candida* spp. To identify the species, genus, and family, we conducted the standard strain *C. glabrata* ATCC 2950 test in line with the CLSI guideline and the manufacturer's instructions.

3. Result

Over a ten-year period from 2009 to 2018, there were a total of 717,996 blood culture referrals, out of which 54,739 tested positive, indicating a positivity rate of 7.6% (**Table 1**). Out of all the culture-positive cases, 3,693 were identified as fungal, and the isolation rate was estimated to be 6.6%. *Candida* accounted for 3,533 fungal positives, excluding mold and *Cryptococcus*, with an isolation rate of 6.4%. The number of *Candida* cases identified and categorized by patients, eliminating duplicates, was 1,036.

Candida albicans represented 33.8% of the isolates, with 350 isolates identified from 1,053 patients, succeeded by *Candida tropicalis* which had 296 isolates (28.6%) from 1,126 patients, followed by *Candida glabrata* with 205 isolates (19.8%) from 587 patients. *Candida parapsilosis* was detected in 81 (7.8%) of 390 patients, followed by *Candida krusei* in 41 (4.0%) of 183 patients. Other species of *Candida* were discovered in 17 (2.5%) of 70 patients, while unidentified yeast-like organisms (UIYLO) were found in 37 (3.6%) of 126 patients (**Table 2** and **Figure 1**).

Table 3 and **Figure 2** present a comparison of the *Candida* spp. isolation frequency split into early (2009–2013) and late (2014–2018) five-year periods. During the early period, 1,733 *Candida* spp. were isolated from 485 patients, whereas for the latter period, 1,800 *Candida* spp. were isolated from 551 patients. *C. albicans* was the most common causative agent of candidemia during the early period as it was responsible for 164 cases (33.9%). Subsequently, *C. tropicalis* had 149 cases (30.6%), *C. glabrata* had 87 cases (18.0%), *C. parapsilosis* had 40 cases (8.3%), and

Table 1. Numerical data positive rate on bacteria and fungi that were isolated from blood cultures in 2009–2018

Year	Number of blood culture	Number of positive vials (%)	Number of fungal positive vials (%)	Number of fungal positive patients
2009	66,980	4,967 (7.4)	271 (5.5)	76
2010	66,142	4,508 (6.8)	281 (6.2)	83
2011	65,731	4,654 (7.1)	310 (6.7)	98
2012	72,462	5,184 (7.2)	451 (8.7)	100
2013	71,355	5,537 (7.8)	420 (7.6)	128
2014	76,267	5,540 (7.3)	333 (6.0)	114
2015	66,227	4,983 (7.5)	294 (5.9)	94
2016	77,520	6,117 (7.9)	344 (5.6)	97
2017	77,404	6,667 (8.6)	365 (5.5)	122
2018	77,908	6,582 (8.4)	464 (7.0)	124
Total	717,996	54,739 (7.6)	3,533 (6.4)	1,036

C. krusei had 22 cases (4.5%). During the latter half of the year, 186 patients had *C. albicans* strains (33.7%), accompanied by 147 patients with *C. tropicalis* strains (26.8%), 118 patients had *C. glabrata* strains (21.4%), 41 patients had *C. parapsilosis* strains (7.4%), and 19 patients had *C. krusei* strains (3.4%). Notably, there was no alteration in the relative frequencies of these strains. Meanwhile, the isolation rate of *C. albicans* remained constant between the first and second halves of the year, although *C. glabrata* saw a 3.4% increase. On the contrary, there has been a decline in the frequency of isolation of each strain, specifically for *C. tropicalis* (3.8%), *C. krusei* (1.1%), and *C. parapsilosis* (0.9%).

Table 2. Comparison of the number of specimens and patients by *Candida* species that were isolated from blood cultures in 2009–2018

Organisms	Number positive by years [specimen (positive patients)]										Total	%
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018		
C. albicans	54 (25)	111 (34)	111 (37)	135 (37)	99 (31)	105 (33)	78 (35)	128 (41)	125 (45)	107 (32)	1,053 (350)	29.8 (33.8)
C. tropicalis	137 (30)	95 (27)	98 (25)	122 (28)	155 (39)	134 (34)	89 (26)	66 (20)	68 (28)	162 (39)	1,126 (296)	31.9 (28.6)
C. glabrata	33 (8)	37 (12)	66 (25)	75 (16)	68 (26)	42 (23)	49 (23)	40 (18)	64 (24)	113 (30)	587 (205)	16.6 (19.8)
C. parapsilosis	24 (7)	21 (7)	16 (4)	47 (8)	42 (14)	9 (4)	65 (5)	47 (5)	90 (17)	29 (10)	390 (81)	11.0 (7.8)
C. krusei	19 (4)	14 (1)	6 (2)	42 (5)	39 (10)	8 (5)	4 (2)	5 (2)	10 (3)	36 (7)	183 (41)	5.2 (4.0)
C. lusitaniae			1 (1)	3 (2)		14 (4)		13 (2)		2 (1)	33 (10)	0.9 (1.0)
C. guilliermondii		1 (1)	1 (1)						2 (2)	12 (4)	16 (8)	0.5 (0.8)
C. utilis			8 (1)	3 (1)							11 (2)	0.3 (0.2)
C. dubliniensis			1 (1)			2 (1)					3 (2)	0.1 (0.2)
C. kefyr	1 (1)								1 (1)		2 (2)	0.1 (0.2)
C. pelliculosa			2 (1)			1 (1)					3 (2)	0.1 (0.2)
UIYLO	3 (1)	2 (1)		24 (3)	17 (8)	18 (9)	9 (3)	45 (9)	5 (2)	3 (1)	126 (37)	3.5 (3.5)
Total	271 (76)	281 (83)	310 (98)	451(100)	420(128)	333(114)	294(94)	344 (97)	365(122)	464 (124)	3,533 (1,036)	100 (100)

Abbreviation: UIYLO, unidentified yeast like organisms

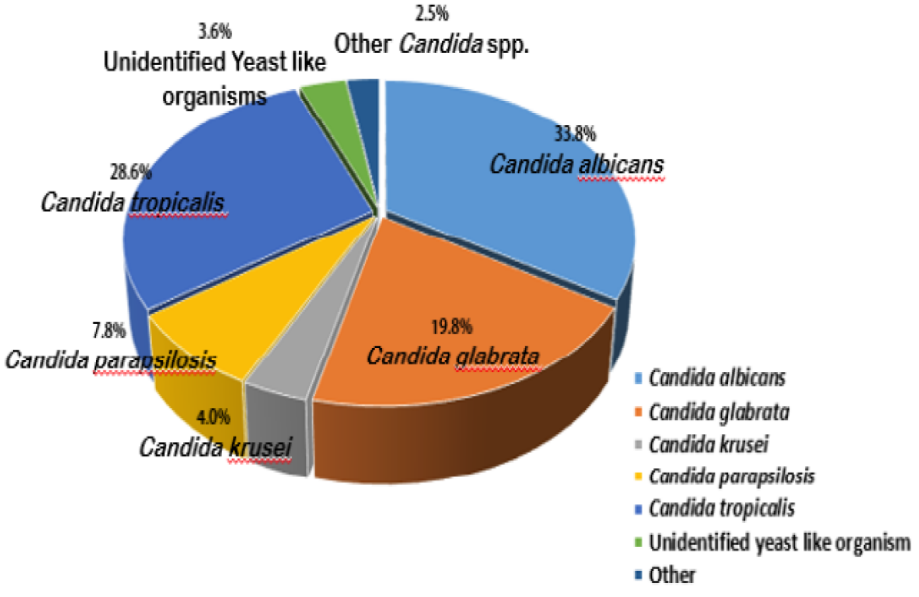

Figure 1. Isolation rate of *Candida* spp. isolated from blood cultures in 2009–2018

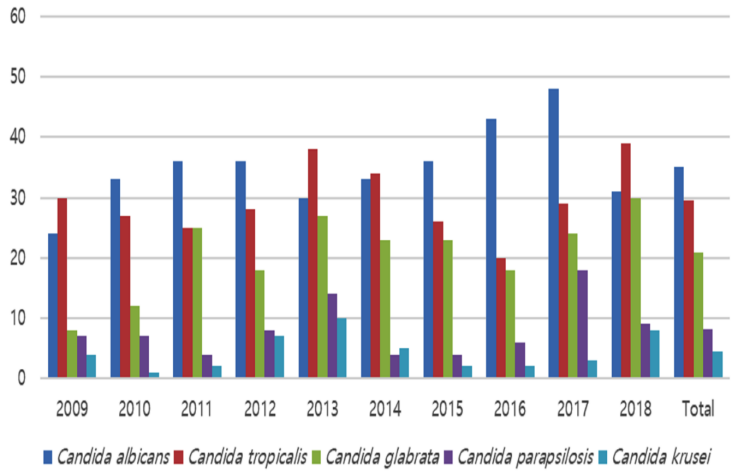

Figure 2. Isolation rate by year of *Candida* spp. isolated from blood cultures in 2009–2018

Table 3. Distribution of 3,533 *Candida* species isolated from 1,036 Candidemia patients in 2009–2013 and 2014–2018 [N (%)]

Organisms	Patients		Isolate		Total	
	2009–2013	2014–2018	2009–2013	2014–2018	Patients	Isolate
C. albicans	164 (33.9)	186 (33.7)	510 (29.5)	543 (30.7)	350 (33.8)	1,053 (30.1)
C. tropicalis	149 (30.6)	147 (26.8)	607 (35.1)	519 (29.3)	296 (28.6)	1,126 (32.2)
C. glabrata	87 (18.0)	118 (21.4)	279 (16.1)	308 (17.4)	205 (19.8)	587 (16.8)
C. parapsilosis	40 (8.3)	41 (7.4)	150 (8.7)	240 (13.6)	81 (7.8)	390 (11.1)
C. krusei	22 (4.5)	19 (3.4)	120 (6.9)	63 (3.6)	41 (4.0)	183 (5.2)
UIYLO	13 (2.6)	24 (4.4)	46 (2.6)	80 (4.1)	37 (3.6)	126 (3.5)
Others	10 (2.1)	16 (2.9)	21 (1.1)	47 (1.0)	26 (2.4)	68 (1.1)
Total	485 (100)	551 (100)	1,733 (100)	1,800 (100)	1,036 (100)	3,533 (100)

Abbreviation: UIYLO, unidentified yeast like organisms

Isolation rates were determined by age. A total of 0.6% of isolation occurred in the < 1 year age group and 6.5% in the 1–10 age group. A slight increase in the isolation rate was observed as the age increased, with 1.2% in the 11–20 age group, 3.1% in the 21–30 age group, 4.9% in the 31–40 age group, and 7.3% in the 41–50 age group. The highest increase in isolation rates was observed in the 51–60 age group, with 16.0%, followed by 23.4% in the 61–70 age group and 22.9% in the 71–80 age group. The isolation rate ranged from 1.2% in the 11–20 age group to 23.4% in the 61–70 age group, which was the highest among all age groups. In the age of under 1 year, two strains of *C. albicans*, *C. glabrata*, and *C. parapsilosis* each were isolated. More specifically, in the age group of 1–30 years, *C. parapsilosis* had a higher prevalence rate than the other age groups at 31.3%, 16.7%, and 18.8%, respectively. However, *C. parapsilosis* was not isolated in the 31–50 age group, while the isolation rate of *C. glabrata* in this age group was high. As for the > 80-year-old age group, the isolation rate of *C. glabrata* was 27.2%, which was higher than the average of 19.8% (**Table 4**).

Upon gender analysis, the isolation frequency was found to be 40.3% in females with 417 cases and 59.7% in males with 619 cases, with a 19.5% increase in male isolation. Most species had been isolated from males, except for *C. krusei*, which had a 60.9% isolation rate in females with 25 cases and 39.0% in males with 16 cases, resulting in 21.9% higher isolation rate in females. *C. albicans* was isolated from 143 females (40.9%) and 207 males (59.1%), with a male predominance of 18.2%. Similarly, *C. tropicalis* was isolated in 114 females (38.5%) and 182 males (61.5%), representing a 23.0% higher incidence in males. Furthermore, *C. glabrata* was detected in 84 females (41.0%) and 121 males (59.0%), indicating an 18.0% greater prevalence in males, and *C. parapsilosis* was found in 29 females (35.8%) and 52 males (64.2%), signifying a 28.4% higher incidence rate in males (**Table 5**).

Table 4. Isolation rate of *Candida* species by age group of patients [N (%)]

Organisms	Age groups										
	< 1	**1–10**	**11–20**	**21–30**	**31–40**	**41–50**	**51–60**	**61–70**	**71–80**	**> 80**	**Total (%)**
C. albicans	2 (33.3)	21 (31.3)	4 (33.2)	12 (37.5)	19 (37.3)	21 (27.6)	56 (33.7)	83 (34.3)	80 (33.8)	52 (35.4)	350 (33.8)
C. tropicalis	-	8 (11.9)	2 (16.7)	6 (18.8)	15 (29.4)	23 (30.3)	51 (30.7)	67 (27.7)	82 (34.6)	42 (28.6)	296 (28.6)
C. glabrata	2 (33.3)	6 (9.0)	2 (16.7)	5 (15.6)	11 (21.6)	21 (27.6)	27 (16.3)	49 (20.2)	42 (17.7)	40 (27.2)	205 (19.8)
C. parapsilosis	2 (33.3)	21 (31.3)	2 (16.7)	6 (18.8)	-	-	10 (6.0)	16 (6.6)	16 (6.8)	8 (5.4)	81 (7.8)
C. krusei	-	1 (1.5)	2 (16.7)	1 (3.1)	5 (9.8)	6 (7.9)	10 (6.0)	11 (4.5)	4 (1.7)	1 (0.7)	41 (4.0)
UIYLO	-	9 (13.4)	-	1 (3.1)	-	3 (3.9)	5 (3.0)	11 (4.5)	6 (2.5)	2 (1.4)	37 (3.6)
Others											
C. dubliniensis					1 (2.0)			1 (0.4)			2 (0.2)
C. guilliermondii						1 (1.3)	3 (1.8)		4 (1.7)		8 (0,8)
C. kefyr				1 (3.1)					1 (0.4)		2 (0.2)
C. lusitaniae		1 (1.5)				1 (1.3)	2 (1.2)	4 (1.7)		2 (1.4)	10 (1.0)
C. pelliculosa							1 (0.6)		1 (0.4)		2 (0.2)
C. utilis							1 (0.6)		1 (0.4)		2 (0.2)
Total	6 (0.6)	67 (6.5)	12 (1.2)	32 (3.1)	51 (4.9)	76 (7.3)	166 (16.0)	242 (23.4)	237 (22.9)	147 (14.2)	1,036 (100)

Abbreviation: UIYLO, unidentified yeast like organisms

Table 5. Isolation rate of *Candida* species by gender in patients

Organisms	Positive patients (%)		
	Female	**Male**	**Total**
C. albicans	143 (40.9)	207 (59.1)	350 (100)
C. tropicalis	114 (38.5)	182 (61.5)	296 (100)
C. glabrata	84 (41.0)	121 (59.0)	205 (100)
C. parapsilosis	29 (35.8)	52 (64.2)	81 (100)
C. krusei	25 (60.9)	16 (39.0)	41 (100)
UIYLO	10 (27.0)	27 (73.1)	37 (100)
Others			
C. dubliniensis	2 (100)		2 (100)
C. guilliermondii	3 (37.5)	5 (62.5)	8 (100)
C. kefyr	1 (50)	1 (50)	2 (100)
C. lusitaniae	4 (40)	6 (60)	10 (100)
C. pelliculosa	1 (50)	1 (50)	2 (100)
C. utilis	1 (50)	1 (50)	2 (100)
Total	417 (40.3)	619 (59.7)	1,036 (100)

Abbreviation: UIYLO, unidentified yeast like organisms

Upon analysis by ward, it was found that in the emergency department, *C. albicans* was present in 36 cases (36.0%), *C. glabrata* in 21 cases (21.0%), *C. tropicalis* in 21 cases (21.0%), and *C. parapsilosis* in 16 cases (16.0%). Similarly, in the general ICU, there were 85 (42.5%) patients with *C. albicans*, 52 (26.0%) patients with *C. glabrata*, and 35 (17.5%) patients with *C. tropicalis* detected. In the neonatal intensive care unit, 15 cases of *C. parapsilosis* were isolated at a rate 34.1% higher than the overall average rate. In the cancer hospital intensive care unit, the rate of *C. tropicalis* isolation was 33.5%, followed by *C. albicans* at 33.0%, and *C. glabrata* at 18.8%, all above the overall average rate. In the cancer hospital wards, *C. tropicalis* was isolated in 122 cases (39.0%), which exceeded the overall average isolation rate. *C. albicans* was isolated in 80 cases (25.6%), followed by *C. glabrata*, which was isolated in 50 cases (16.0%). In general wards, 53 cases (36.8%) of *C. albicans* were isolated, while *C. tropicalis* and *C. glabrata* were isolated in 36 (25.0%) and 30 cases (20.8%), respectively. The rates of isolation for *C. parapsilosis*, *C. albicans*, and *C. glabrata* were notably greater in the emergency departments and general intensive care units compared to the average isolation rates, and *C. parapsilosis* was particularly prevalent in neonatal intensive care units. However, no isolation were detected for *C. tropicalis* and *C. krusei*. Furthermore, the prevalence of *C. tropicalis* was significantly higher in the intensive care units of cancer wards and in cancer wards, indicating an overall high prevalence in cancer hospitals. Conversely, *C. albicans* exhibited high prevalence in the ICUs and general wards (**Table 6**).

4. Discussion

There are approximately 100 known *Candida* species. However, only a few species are capable of infecting humans, with *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* accounting for the majority of candidemia cases. This study found that these five species were responsible for 93.9% of the cases. In the 1980s and 1990s, *C. albicans* was the primary cause of candidemia on a global scale; however, its prevalence has decreased since the 2000s, and non-*albicans Candida* strains, including *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. glabrata*, have become more commonly associated with infections [17,18]. In

Table 6. Isolation rate of *Candida* species by wards

Organisms	Positive patients (%)						
	ER	ICU	NICU	CWICU	CW	GW	Total
C. albicans	36 (36.0)	85 (42.5)	15 (34.1)	81 (33.0)	80 (25.6)	53 (36.8)	350 (33.8)
C. tropicalis	21 (21.0)	35 (17.5)		82 (33.5)	122 (39.0)	36 (25.0)	296 (28.6)
C. glabrata	21 (21.0)	52 (26.0)	6 (13.6)	46 (18.8)	50 (16.0)	30 (20.8)	205 (19.8)
C. parapsilosis	16 (16.0)	13 (6.5)	15 (34.1)	11 (4.5)	16 (5.1)	10 (6.9)	81 (7.8)
C. krusei	1 (1.0)	9 (4.5)		14 (5.7)	17 (5.4)		41 (4.0)
UIYLO	1 (1.0)	4 (2.0)	8 (18.2)	8 (3.3)	8 (2.6)	8 (5.6)	37 (3.6)
Others							
C. dubliniensis		1 (0.5)			1 (0.4)		2 (0.2)
C. guilliermondii	1 (1.0)	1 (0.5)			2 (0.7)	4 (2.8)	8 (0.8)
C. kefyr				1 (0.4)		1 (0.7)	2 (0.2)
C. lusitaniae	2 (2.0)			1 (0.4)	5 (1.4)	2 (1.4)	10 (0.9)
C. pelliculosa	1 (1.0)				1 (0.4)		2 (0.2)
C. utilis				1 (0.4)	1 (0.4)		2 (0.2)
Total	100 (9.7)	200 (19.3)	44 (4.3)	245 (23.6)	303 (29.2)	144 (13.9)	1,036 (100)

Abbreviation: UIYLO, unidentified yeast like organisms; ER, emergency room; ICU, intensive care unit; NICU, neonatal intensive care unit; CWICU, cancer ward intensive care unit; CW, cancer ward; GW, general ward

many regions, *C. albicans* remains the leading cause of candidemia; however, *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* are gradually edging out *C. albicans* as the second most prevalent causative agent [19,20]. In this study, the results showed that *C. albicans* was the most prevalent fungus with a rate of 33.8% (n = 350), closely followed by *C. tropicalis* at 28.6% (n = 296) as the second most common causative agent. Furthermore, non-*albicans Candida* species, excluding *C. albicans*, constituted 66%. Lamoth *et al.* (2019) reported that *C. glabrata* ranks as the second most prevalent non-*albicans Candida* species in the UK, Europe, and Australia, but ranks third or fourth after *C. tropicalis* and *C. parapsilosis* in Asia and Latin America. The aforementioned conclusion is supported by numerous studies conducted worldwide [21]. In 2013, Won *et al.* conducted a study of fungal distribution across 12 hospitals in Korea. Their findings indicated the top three isolated species in descending order were *C. albicans* (41.7%), *C. parapsilosis* (17.8%), and *C. glabrata* (14.4%) [22]. In 2017, Kim *et al.* conducted a study over a 20-year period within a single tertiary medical center. Their results showed that *C. albicans* (40.8%) was the most frequently isolated species, followed by *C. parapsilosis* (24.1%) and *C. tropicalis* (13.2%), with *C. glabrata* (12.8%) following suit [23]. The study found that *C. albicans* accounted for 33.8% of the samples, followed by *C. tropicalis* at 28.1%, *C. glabrata* at 19.7%, and *C. parapsilosis* at 7.8%. These results aligned with prior research conducted in Asia and South America. Additionally, the data revealed a 3.4% increase in *C. glabrata* and a 3.8% decrease in *C. tropicalis* during the second period of the study, indicating a rising detection rate for *C. glabrata*. The rising prevalence of *C. glabrata* is a global phenomenon of clinical significance due to its strong correlation with antifungal resistance. A recent large-scale surveillance study carried out across four major US cities revealed a surge in echinocandin-resistant *C. glabrata* [14]. In 2021, a study by Won *et al.* in Korea confirmed that echinocandin resistance increased after 2013 with 1.4% (n = 1) in 2013, 2.7% (n = 3) in 2015, 3.3% (n = 4) in 2016, 2.3% (n = 4) in 2017, and 2.4% (n = 4) in 2018, where a total of 1,158 *C. glabrata* were analyzed from 19 university hospitals in Korea from January 2008 to December 2018 [24]. The rise of *C. glabrata* in comparison to other strains in the ICU within this study is worrying and necessitates further investigation into echinocandin resistance. Disparities in the distribution of *Candida* spp. may correlate with local ecology and are crucial as modifications in species-specific antifungal susceptibility patterns can impact the efficacy of treatment. Furthermore, the primary isolation of certain species, namely *C. parapsilosis*, may imply a requirement for a review of hospital infection control protocols. Early fungal identification and timely initiation of suitable treatment may positively influence patient outcomes and prognosis, while delayed appropriate treatment may have a negative impact on patient outcomes and prognosis [25].

Clinically, the identification of *Candida* at the species level is significant, as it equips clinicians with valuable information for guiding patient management and antifungal therapy. Species-level identification is necessary to create proper therapeutic guidelines as certain fungi are innately resistant to particular medications. Furthermore, even within the same species, certain strains may have differing susceptibility profiles to antifungal agents, which can impact patient outcomes [26]. While not isolated in this study, *C. auris* was initially reported in 2009 and has rapidly disseminated to numerous countries across multiple continents, presenting a critical clinical concern. *C. auris* displays low susceptibility to azole antifungals and frequently presents with multidrug resistance [27]. The WHO has documented a retrospective examination of 54 patient histories, indicating a 59% mortality rate and 90% fluconazole resistance [28]. In South Korea, fifty-seven cases of *C. auris* infection were isolated from ear secretions and four cases from blood samples over the past two decades. These cases were primarily

detected in the external auditory canal rather than candidemia. Although this situation is not presently severe, there is potential for outbreaks in intensive care units at any time, which could result in serious consequences [29]. In short, it is crucial to investigate the frequency of identifying and isolating *Candida* species in patients with candidemia. This study's findings are relevant to the use of antifungal drugs and infection control policies implemented across various hospitals and regions. Hence, this research holds significant value in beginning adequate treatment for patients showing symptoms of fungal infections and developing guidelines on patient management and antifungal therapy. It is crucial to establish and regulate the occurrence and frequency of infections. Additionally, it is imperative to plan for the possibility of emerging fungal infections by implementing a methodical and consistent system for monitoring hospital infections and operational surveillance.

5. Conclusion

Candidemia, a leading contributor to illness and death, continues to pose a significant threat to hospital patients and inflates healthcare expenditure. This study analyzed 3,533 cases of *Candida* isolates from blood cultures in Hospital S between 2009 and 2018 by frequency of isolation, year, gender, age, and ward. During the study period, there were 717,996 blood culture referrals, of which 54,739 were culture positive, indicating a positive rate of 7.6%. Moreover, the isolation rate of *Candida* was found to be 6.4%, with 3,533 isolates detected from 1,036 patients. The distribution of *Candida* species included *C. albicans* (33.8%), *C. tropicalis* (28.6%), *C. glabrata* (19.8%), *C. parapsilosis* (7.8%), and *C. krusei* (4.0%). Lastly, it was observed that the frequency of isolation of *C. tropicalis* decreased by 3.8%, whereas *C. glabrata* increased by 3.4%. After the age of fifty, the rate of isolation increased, with *C. parapsilosis* (31.3%) discovered in the 1–10 age group, *C. tropicalis* (30.3%) and *C. glabrata* (27.6%) in the 41–50 age group, and *C. tropicalis* (28.6%) in the > 80 age group. *C. krusei* was found at a considerably high frequency in females (60.9%). Therefore, it is essential to establish a regular and ongoing nosocomial infection control system to continually track the distribution of *Candida* species and promptly identify them to direct proper treatment and antifungal therapy.

Disclosure statement

The authors declare no conflict of interest.

References

[1] López Dupla M, Martínez JA, Vidal F, et al., 2005, Clinical Characterization of Breakthrough Bacteraemia: A Survey of 392 Episodes. J Intern Med, 2005(258): 172–180. https://doi.org/10.1111/j.1365-2796.2005.01513.x

[2] Balk RA, 2000, Severe Sepsis and Septic Shock. Definitions, Epidemiology, and Clinical Manifestations. Crit Care Clinics, 2000(16): 179–192. https://doi.org/10.1016/s0749-0704(05)70106-8

[3] Goto M, Al-Hasan MN, 2013, Overall Burden of Bloodstream Infection and Nosocomial Bloodstream Infection in North America and Europe. Clin Microbiol Infect, 19(6): 501–509. https://doi.org/10.1111/1469-0691.12195

[4] Antinori S, Milazzo L, Sollima S, et al., 2016, Candidemia and Invasive Candidiasis in Adults: A Narrative Review. Eur J InternMed, 2016(34): 21–28. https://doi.org/10.1016/j.ejim.2016.06.029

[5] Pappas PG, Kauffman CA, Andes DR, et al., 2016, Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis, 62(4): e1–e50. https://doi.org/10.1093/cid/civ933

[6] Marchetti O, Bille J, Fluckiger U, et al., 2004, Epidemiology of Candidemia in Swiss Tertiary Care Hospitals: Secular Trends, 1991–2000. Clin Infect Dis, 38(3): 311–320. https://doi.org/10.1086/380637

[7] Horn DL, Fishman JA, Steinbach WJ, et al., 2007, Presentation of the PATH Alliance Registry for Prospective Data Collection and Analysis of the Epidemiology, Therapy, and Outcomes of Invasive Fungal Infections. Diagn Microbiol Infect Dis, 59(4): 407–414. https://doi.org/10.1016/j.diagmicrobio.2007.06.008

[8] Falagas ME, Roussos N, Vardakas KZ, 2010, Relative Frequency of *albicans* and the Various Non-*albicans Candida* spp Among Candidemia Isolates from Inpatients in Various Parts of the World: A Systematic Review. Int J Infect Dis, 14(11): e954–e966. https://doi.org/10.1016/j.ijid.2010.04.006

[9] Kim JS, Gong SY, Kim JW, et al., 2019, Antimicrobial Susceptibility Patterns of Microorganisms Isolated from Blood Culture During the Last 8 Years: 2010–2017. Korean J Clin Lab Sci, 2019(51): 155–163. https://doi.org/10.15324/kjcls.2019.51.2.155

[10] Kett DH, Azoulay E, Echeverria PM, et al., 2011, Extended Prevalence of Infection in ICU Study (EPIC II) Group of Investigators. *Candida* Bloodstream Infections in Intensive Care Units: Analysis of the Extended Prevalence of Infection in Intensive Care Unit Study. Crit Care Med, 39(4): 665–670. https://doi.org/10.1097/CCM.0b013e318206c1ca

[11] Colombo AL, Guimaraes T, Sukienik T, et al., 2014, Prognostic Factors and Historical Trends in the Epidemiology of Candidemia in Critically Ill Patients: An Analysis of Five Multicenter Studies Sequentially Conducted over a 9-Year Period. Intensive Care Med, 2014(40): 1489–1498. https://doi.org/10.1007/s00134-014-3400-y

[12] Falagas ME, Apostolou KE, Pappas VD, 2006, Attributable Mortality of Candidemia: A Systematic Review of Matched Cohort and Case-Control Studies. Eur J Clin Microbiol Infect Dis, 2006(25): 419–425. https://doi.org/10.1007/s10096-006-0159-2

[13] Taei M, Chadeganipour M, Mohammadi R, 2019, An Alarming Rise of Non-*albicans Candida* Species and Uncommon Yeasts in the Clinical Samples; A Combination of Various Molecular Techniques for Identification of Etiologic Agents. BMC Res Notes, 2019(12): 779. https://doi.org/10.1186/s13104-019-4811-1

[14] Diekema D, Arbefeville S, Boyken L, et al., 2012, The Changing Epidemiology of Healthcare-Associated Candidemia Over Three Decades. Diagn Microbiol Infect Dis, 73(1): 45–48. https://doi.org/10.1016/j.diagmicrobio.2012.02.001

[15] Arendrup MC, Sulim S, Holm A, et al., 2011, Diagnostic Issues, Clinical Characteristics, and Outcomes for Patients with Fungemia. J Clin Microbiol, 49(9): 3300–3308. https://doi.org/10.1128/JCM.00179-11

[16] Ding X, Yan D, Sun W, et al., 2015, Epidemiology and Risk Factors for Nosocomial non-*Candida albicans* Candidemia in Adult Patients at a Tertiary Care Hospital in North China. Med Mycol, 53(7): 684–690. https://doi.org/10.1093/mmy/myv060

[17] Cleveland AA, Harrison LH, Farley MM, et al., 2015, Declining Incidence of Candidemia and the Shifting Epidemiology of *Candida* Resistance in Two US Metropolitan Areas, 2008–2013: Results from Population-Based Surveillance. PLoS One, 2015(10): e0120452. https://doi.org/10.1371/journal.pone.0120452

[18] Hesstvedt L, Gaustad P, Andersen CT, et al., 2015, Twenty-Two Years of Candidaemia Surveillance: Results from a Norwegian National Study. Clin Microbiol Infect, 21(10): 938–945. https://doi.org/10.1016/j.cmi.2015.06.008

[19] Kumar S, Kalam K, Ali S, et al., 2014, Frequency, Clinical Presentation and Microbiological Spectrum of Candidemia in a Tertiary Care Center in Karachi, Pakistan. J Pak Med Assoc, 2014(64): 281–285.

[20] Tang JL, Kung HC, Lei WC, et al., 2015, High Incidences of Invasive Fungal Infections in Acute Myeloid Leukemia

Patients Receiving Induction Chemotherapy Without Systemic Antifungal Prophylaxis: A Prospective Observational Study in Taiwan. PLoS One, 2015(10): e0128410. https://doi.org/10.1371/journal.pone.0128410

[21] Lamoth F, Lockhart SR, Berkow EL, et al., 2018, Changes in the Epidemiological Landscape of Invasive Candidiasis. J Antimicrob Chemother, 2018(73): i4–i13. https://doi.org/10.1093/jac/dkx444

[22] Won EJ, Shin JH, Lee WK, et al., 2013, Distribution of Yeast and Mold Species Isolated from Clinical Specimens at 12 Hospitals in Korea During 2011. Ann Clin Microbiol, 16(2): 92–100. https://doi.org/10.5145/ACM.2013.16.2.92

[23] Kim D, Hwang GY, Yoo G, et al., 2017, Trend of Prevalence and Antifungal Drug Resistance of *Candida* Species Isolated from Candidemia Patients at a Tertiary Care Hospital During Recent Two Decades. Ann Clin Microbiol, 2017(20): 53–62.

[24] Won EJ, Choi MJ, Kim MN, et al., 2021, Fluconazole Resistant *Candida glabrata* Bloodstream Isolates, South Korea, 2008–2018. Emerg Infect Dis, 27(3): 779–788. https://doi.org/10.3201/eid2703.203482

[25] Chamilos G, Lewis RE, Kontoyiannis DP, 2008, Delaying Amphotericin B-Based Frontline Therapy Significantly Increases Mortality Among Patients with Hematologic Malignancy who Have Zygomycosis. Clin Infect Dis, 47(4): 503–509. https://doi.org/10.1086/590004

[26] Gilgado F, Serena C, Cano J, et al., 2006, Antifungal Susceptibilities of the Species of the *Pseudallescheria boydii* Complex. Antimicrob Agents Chemother, 50(12): 4211–4213. https://doi.org/10.1128/AAC.00981-06

[27] Chowdhary A, Prakash A, Sharma C, et al., 2018, A Multicentre Study of Antifungal Susceptibility Patterns Among 350 *Candida auris* Isolates (2009–2017) in India: Role of the *ERG11* and *FKS1* Genes in Azole and Echinocandin Resistance. J Antimicrob Chemother, 73(4): 891–899. https://doi.org/10.1093/jac/dkx480

[28] World Health Organization, 2014, Antimicrobial Resistance Global Report on Surveillance 2014, viewed January 14, 2022, https://apps.who.int/iris/bitstream/handle/10665/112647/WHO_HSE_PED_AIP_2014.2_eng.pdf

[29] Kwon YJ, Shin JH, Byun SA, et al., 2019, *Candida auris* Clinical Isolates from South Korea: Identification, Antifungal Susceptibility, and Genotyping. J Clin Microbiol, 57(4): e01624–18. https://doi.org/10.1128/JCM.01624-18