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Comparison of fungemia caused by *Candida* and non-*Candida* rare yeasts: a retrospective study from a tertiary care hospital

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Abstract

Although *Candida* species are the most common cause of fungemia, non-*Candida* rare yeasts (NCY) have been increasingly reported worldwide. Although the importance of these yeast infections is recognized, current epidemiological information about these pathogens is limited, and they have variable antifungal susceptibility profiles. In this study, we aimed to evaluate the clinical characteristics for fungemia caused by NCY by comparing with candidemia. The episodes of NCY fungemia between January 2011 and August 2023 were retrospectively evaluated in terms of clinical characteristics, predisposing factor, and outcome. In addition, a candidemia group, including patients in the same period was conducted for comparison. Antifungal susceptibility tests were performed according to the reference method. A total of 85 patients with fungemia episodes were included: 25 with NCY fungemia and 60 with candidemia. Fluconazole had high minimal inhibitory concentration (MIC) values against almost all NCY isolates. The MIC values for voriconazole, posaconazole, and amphotericin B were $\leq$ 2 μg/ml, and for caspofungin and anidulafungin were $\geq$ 1 μg/ml against most of isolates. Hematological malignancies, immunosuppressive therapy, neutropenia and prolonged neutropenia, polymicrobial bacteremia/fungemia, preexposure to antifungal drugs, and breakthrough fungemia were associated with NCY fungemia, whereas intensive care unit admission, diabetes mellitus, urinary catheters, and total parenteral nutrition were associated with candidemia. In conclusion, the majority of fungemia due to NCY species was the problem, particularly in hematology units and patients with hematological malignancy. Preexposure to antifungal drugs likely causes a change in the epidemiology of fungemia in favor of non-*albicans Candida* and/or NCY.

Lay summary

Among all fungemia episodes, hematological malignancies, immunosuppressive therapy, neutropenia, and preexposure to antifungals were risk factors for non-*Candida* yeast fungemia; diabetes mellitus, urinary catheters, and total parenteral nutrition were risks for candidemia.

Key words: *Candida*, candidemia, fungemia, non-*Candida*, rare yeast.

Introduction

Timely diagnosis of invasive fungal diseases (IFDs) is crucial to guide appropriate treatment, improve patient outcomes, and reduce healthcare costs.[1] Detection of pathogenic fungi by histopathological examination in tissue samples or culture methods using sterile specimens is considered as the gold standard for definitive diagnosis of IFDs. However, obtaining a clinical specimen for histopathological examination requires invasive procedures, which are often infeasible for immunocompromised and/or critically ill patients. Conventional culture methods have insufficient sensitivity and prolonged turnaround time. However, identification of the isolated species is important for epidemiological and clinical appreciation;[2] moreover, antifungal susceptibility characteristics vary depending on the genus and the species.[3] Unfortunately, phenotypic identification methods and biochemical kits that were widely used in routine clinical laboratories are often inadequate for species identification of non-*Candida* rare yeast (NCY) isolates and require confirmation with molecular (i.e., DNA/PCR) or proteomic (matrix-assisted laser desorption ionization time-of-flight mass spectrometry, MALDI-TOF MS) methods; most likely, MALDI-TOF MS systems will replace them for yeast identification.[2] In the "global guideline for the diagnosis and management of rare yeast infections," phenotypic identification methods and MALDI-TOF MS are moderately supported, while molecular approaches are strongly supported for species identification of rare yeasts. Specific serological markers for NCY infections are not available, and data on the diagnostic use of serum 1,3-β-D-glucan testing is limited; it is weakly supported.[2]

Candida species, especially *C. albicans*, are the most common cause of fungemia worldwide. Although NCYs such as *Trichosporon*, *Rhodotorula*, *Magnusiomyces*, *Geotrichum*, *Saccharomyces*, and *Saprochaete* account for a limited number of fungemia, they are increasingly encountered and recognized as a growing problem. The rates of fungemia due to NCYs have been reported to range from 1.1% to 10.0%, depending on the clinics and the patient spectrum in the re-

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cent years.[4–8] The increasing number of NCY infections has been associated with the increase of severely immunocompromised patients, as well as extensive use of antifungals.[2,9] In addition, prolonged hospitalizations, transplantations, the widespread use of central venous catheters (CVC), total parenteral nutrition (TPN), and broad-spectrum antibiotics may also contribute to this increase. Since the NCYs largely have intrinsic resistance or reduced susceptibility to specific antifungal agents, such as fluconazole and echinocandins, which are commonly used for prophylaxis in hematological patients, it creates a risk of breakthrough infection for these patients.[2] Most NCYs may be colonizers of human skin and mucosal surfaces. Therefore, NCYs may be isolated from the cultures of non-sterile specimen without any infection. However, increasing number of severely immunocompromised patients and/or extensive use of antifungals may result a rise in NCY infections. Even if these yeasts have relatively low virulence, the mortality rate in immunocompromised patients is high.[2,6]

NCYs have been associated with serious life-threatening infections in immunocompromised hosts.[4] Although the importance of these yeast infections is recognized, current epidemiological information about these pathogens is limited. Furthermore, the management of these pathogens remains challenging due to difficulties in identification, variability in susceptibility profiles, difficulties in interpretation of susceptibility profiles due to the absence of established clinical breakpoints, and a lack of knowledge about the optimal antifungal therapy regimen.[2] In this study, we aimed to evaluate the clinical characteristics of fungemia caused by rare yeasts other than *Candida* by comparing with those of *Candida* spp. in a single center in Turkey.

Materials and methods

Study population

This study was conducted retrospectively in a 1100-bed tertiary care hospital. The patients with fungemia caused by rare yeasts other than *Candida* (NCY fungemia group) between January 1, 2011 and August 1, 2023 were included. The candidemia group consisted of the patients whose *Candida* species were isolated from index blood culture in the same week (within ± 3 days) with the date of index NCY isolation. Pediatric patients (age < 18 years) were not included in this study.

Patient data

Data regarding demographic characteristics, underlying malignancies, immunosuppressive agent use within 30 days prior to diagnosis of fungemia, neutropenia, catheter use, admission ward and days of hospitalization at the onset of fungemia, intensive care unit (ICU) admission, concomitant infections, antifungal prophylaxis/treatment, the histories of transplantation and gastrointestinal surgery within 3 months prior to fungemia, antibiotic therapy at least 3 days within 30 days prior to the fungemia episode, and outcome were collected from the patients' medical electronical records.

Species identification and antifungal susceptibility testing

Primarily, the colony morphology on Sabouraud's dextrose agar (SDA) and microscopic features on corn meal tween 80 agar were evaluated for the identification of the isolates. The final identification of all isolates was performed on matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics, Germany) using the database of MALDI Biotyper Compass version 4.1.100 containing 10 833 spectra. Since MALDI-TOF MS system has been used in our laboratory since 2020, MALDI-TOF MS has been routinely used for the final identification of all yeast isolates. The isolates before 2020 were routinely identified with API 20C AUX (BioMerieux, France) and stored at −70°C. Before this study, these isolates were subcultured on SDA and their final identification was confirmed with MALDI-TOF MS. The analysis criteria formulated by the manufacturer were used for identification: a score of < 1.7 indicates no identification, a score of 1.7 to 1.99 is considered a low-confidence identifications, and a score of ≥ 2.0 is considered a high-confidence identification. Each isolate was analyzed in triplicate. The scores ≥ 2 were considered for reliable identification. The system was calibrated before each analysis using the strain of *Escherichia coli* DH5. *In vitro* antifungal susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods in document M27-A3.[10]

Definitions

Index blood culture was defined as the first blood culture yielding a yeast-like fungus throughout the study period. NCY fungemia was defined as a blood stream infection (BSI) due to rare opportunistic yeasts by the demonstration of a NCY in the index culture in presence of a clinical picture compatible with fungemia. Neutropenia was defined as an absolute neutrophil count of < 500 cells/μl. Polymicrobial bacteremia/fungemia was defined as the isolation of other bacteria/fungi from the blood within 24 hours of the index blood culture. Breakthrough fungemia was defined as BSI in a patient receiving systemic antifungal therapy for at least 72 hours before the date of the index culture.[6,9]

Statistical analysis

Statistical analyses were performed using SPSS software for Windows version 20.0 (Statistical Package for the Social Sciences, SPSS, Inc., Chicago, IL, USA). Frequency distribution, percentage, mean, median, standard deviation or median, and min-max values were used to evaluate descriptive data. The conformity of the quantitative data to the normal distribution was evaluated with the Kolmogorov–Smirnov and Shapiro–Wilk tests. Since the data did not show normal distribution, Mann–Whitney U was used to analysis comparisons between groups. The Chi-square test was used in the analysis of the qualitative data. Fischer's Exact test was used in the analysis of tables where the expected value was < 5. The significance level was determined as 0.05 in all statistical analyses.

Results

A total of 85 patients with fungemia episodes were included in this study. The isolates of NCY fungemia ($n = 25$) were *Magnusiomyces capitatus* ($n = 7$), *Rhodotorula mucilaginosa* ($n = 6$), *Trichosporon asahii* ($n = 5$), *M. clavatus* ($n = 2$), *Cutaneotrichosporon dermatis* ($n = 2$), *C. mucoides* ($n = 1$), *Geotrichum candidum* ($n = 1$), and *Saccharomyces cerevisiae*

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Table 1. Antifungal susceptibility testing results of non-*Candida* yeast isolates tested.

Isolates (*n*)	MIC range (mean/median)*, μg/ml					
	Fluconazole	Voriconazole	Posaconazole	Caspofungin	Anidulafungin	Amphotericin B
Magnusiomyces capitatus (6)	4–16 (7.2/4)	0.125–2 (0.73/0.38)	2 (2/2)	> 16 (40/38)	> 16 (28/32)	0.5–1 (0.9/1)
Magnusiomyces clavatus (2)	16–32	0.5–1	0.5–2	16	2	1
Rhodotorula mucilaginosa (4)	64–128 (96/96)	0.5–2 (1.25/1.25)	0.25–2 (0.94/0.75)	4–16 (10/10)	2–8 (3.5/2)	0.25–2 (0.75/0.75)
Trichosporon asahii (4)	2–8 (3.5/2)	0.03–0.25 (0.078/0.03)	0.03–0.5 (0.38/0.5)	2–8 (5.5/6)	1–4 (2/1.5)	0.5–1 (0.75/0.75)
Cutaneotrichosporon dermatis (2)	4–8	0.12–0.25	0.03-0.5	0.12–2	0.06–0.5	0.5
Cutaneotrichosporon mucoides (1)	0.5	0.25	0.5	1	0.25	1
Geotrichum candidum (1)	2	1	1	0.5	1	2
Saccharomyces cerevisiae (1)	8	0.06	1	0.125	0.06	0.25

*Mean and median values were calculated for the species with > 2 isolates, and unclear MIC values (>, <) were rounded to the next upper or lower dilution.

($n = 1$). Antifungal susceptibility testing results of NCY isolates tested were summarized in Table 1. Categorical interpretation could not be performed for the antifungal susceptibility profiles of these isolates because there are no established clinical breakpoints yet. Fluconazole had high minimal inhibitory concentration (MIC) values against almost all isolates. The MIC values for voriconazole, posaconazole, and amphotericin B were ≤ 2 μg/ml, and caspofungin and anidulafungin MIC values were ≥ 1 μg/ml against most NCY isolates.

The isolates of candidemia ($n = 60$) were *Candida parapsilosis* ($n = 24$), *C. albicans* ($n = 21$), *Nakaseomyces glabratus* (*C. glabrata*, $n = 9$), *C. tropicalis* ($n = 3$), *Pichia kudriavzevii* (*C. krusei*, $n = 1$), *Kluyveromyces marxianus* (*C. kefyr*, $n = 1$), and *Meyerozyma guilliermondii* (*C. guilliermondii*, $n = 1$). The distribution of *Candida* isolates in this study was consistent with the distribution of candidemia agents in our center; the most common agent of candidemia is *C. parapsilosis*, followed by *C. albicans*, and the rate of non-*albicans* candidemia is almost 67% in our center (unpublished data). The incidence of NCY fungemia was 2.0% among all fungemia episodes ($n = 1136$) determined between 2011 and 2023 in our center.

Demographic and clinical characteristics of all patients are shown in Table 2. The risk factors for NCY fungemia among all fungemia episodes were included hospitalization in hematology/oncology wards, hematological malignancies, immunosuppressive therapy, neutropenia and prolonged neutropenia, polymicrobial bacteremia/fungemia, preexposure to antifungal drugs, and breakthrough fungemia were associated with NCY fungemia compared to candidemia. However, ICU admission, diabetes mellitus, urinary catheters, and TPN were risk factors for candidemia according to fungemia episodes. Furthermore, when non-*albicans* candidemia and NCY fungemia together ($n = 64$) were compared to *C. albicans* candidemia, chemotherapy, neutropenia, and preexposure to antifungal drugs were risk factors for non-*C. albicans* yeasts, and breakthrough fungemia was significantly associated with fungemia caused by non-*C. albicans* yeasts ($P < 0.05$); none of the candidemia caused by *C. albicans* had chemotherapy, neutropenia, preexposure to antifungal drugs, or breakthrough fungemia.

No significant differences were detected among episodes of candidemia, NCY fungemia, or *C. albicans* fungemia in terms of age, gender, history of surgery, days of hospitalization, CVC, presence of candiduria, antibacterial treatment, and mortality (10-day or 30-day) rates in the present study ($P > 0.05$).

Discussion

NCY have increasing interest because they frequently affect immunocompromised or seriously ill patients and are often resistant to certain antifungal agents. This study represents the epidemiological, clinical, and microbiological characteristics of fungemia caused by NCYs and the results of comparison with candidemia in a single tertiary center in Turkey. Most of our NCY isolates causing fungemia were *Magnusiomyces* species and followed by *Rhodotorula mucilaginosa* and *Trichosporon* species. In previous reports, significant differences have been observed among the results of studies in terms of the species distribution.[4–9] It may be related to regional variables, host predisposing factors, frequency use, and choice of antifungal drugs. Therefore, it seems that to make a generalization for the species distribution of the agents of NCY fungemia is difficult.

The lack of species-specific breakpoints to interpret antifungal susceptibility testing results, insufficient data on susceptibility characteristics, and limited treatment experience complicate optimal therapeutic management of fungemia due to NCY. In order to make a comment about antifungal susceptibility testing results of NCY isolates, species-specific breakpoint values of *Candida* spp. established by CLSI were reviewed; fluconazole MIC values ≤ 2 μg/ml and voriconazole MIC values ≤ 0.12 μg/ml are considered as susceptible for *C. albicans, C. tropicalis*, and *C. parapsilosis*.[11] In accordance with previous reports,[6,8,9,12] we obtained elevated MICs to fluconazole for all NCY isolates tested except for one *C. mucoides* isolate. Most of our NCY isolates have MIC values > 2 μg/ml for fluconazole and the isolates of *R. mucilaginosa* exhibited the highest fluconazole MICs (≥ 64 μg/ml). Pfaller et al.[13] showed that *Rhodotorula* spp. ($n = 381$) exhibited > 50% resistance to fluconazole and ≥ 40% resistance to voriconazole by disk diffusion method in a global antifungal surveillance study. They reported that *Rhodotorula* spp. must be considered to be intrinsically resistant to both azole and echinocandin antifungals; thus, neither fluconazole nor echinocandins should be used to treat infections due to *Rhodotorula*, and patients receiving these antifungals may be susceptible to developing breakthrough *Rhodotorula* fungemia.[13] In recent studies, including a limited number

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Table 2. Demographic and clinical characteristics of patients with fungemia.

Characteristics	Fungemia due to			Fungemia due to		
	Non-*Candida* yeasts, *n* = 25	*Candida* spp, *n* = 60	*P*[a]	Non-*albicans Candida* + non-*Candida* yeasts, *n* = 64	*C. albicans*, *n* = 21	*P*[a]
Mean age in years ± SD (range)	60.80 ± 19.21 (20–88)	63.65 ± 13.37 (24–89)	0.436	63.22 ± 16.65 (20–89)	61.57 ± 10.10 (39–78)	0.427
Male gender, *n* (%)	14 (56.0)	34 (56.7)	0.997	36 (56.3)	12 (57.1)	0.943
Admission wards, *n* (%)			**0.007**[b]			0.081
• Hematology/onchology	13 (52.0)	11 (18.3)		22 (34.4)	2 (9.5)	
• Medical (other)	8 (32.0)	36 (60.0)		31 (48.4)	13 (61.9)	
• Surgical	4 (16.0)	13 (21.7)		11 (17.2)	6 (28.6)	
Intensive care unit admission at index culture, *n* (%)	12 (48.0)	44 (73.4)	**0.025**	41 (64.1)	15 (71.4)	0.537
Days of ICU until index culture, median (range)	16 (2–70)	10 (1–86)	0.285	15 (1–86)	7 (1–52)	**0.049**
Malignancy, *n* (%)			**< 0.001**[c]			0.075
• Hematological	12 (48.0)	6 (10.0)		17 (26.6)	1 (4.8)	
• Solid tumor	4 (16.0)	28 (46.7)		21 (32.8)	11 (52.4)	
• None	9 (36.0)	26 (43.3)		26 (40.6)	9 (42.9)	
Diabetes mellitus, *n* (%)	9 (36.0)	45 (75.0)	**0.001**	40 (62.5)	14 (66.7)	0.731
Surgery within 3 months, *n* (%)	4 (16.0)	9 (15.0)	0.907	9 (14.1)	4 (19.0)	0.582
Days of hospitalization until index culture, median (range)	24 (1–73)	18 (1–214)	0.277	23 (1–214)	17 (1–52)	0.145
Immunosuppressive therapy within 30 days prior to index culture, *n* (%)	14 (56.0)	16 (26.7)	**0.010**	26 (40.6)	4 (19.0)	0.073
• Chemotherapy	7 (28.0)	6 (10.0)	**0.036**	13 (20.3)	0 (0.0)	**0.025**
• Corticosteroid	7 (28.0)	13 (21.7)	0.531	16 (25.0)	4 (19.0)	0.577
Days of immunosuppressive therapy, median (range)	7 (1–35)	9 (2–48)	0.566	8 (1–35)	8 (2–48)	0.907
Neutropenia at diagnosis, *n* (%)						
• < 500	9 (36.0)	3 (5.0)	**0.001**	12 (18.8)	0 (0.0)	**0.032**
• < 100	8 (32.0)	2 (3.3)	**0.001**	10 (15.6)	0 (0.0)	**0.046**
Days of neutropenia until index culture, median (range)	24 (3–57)	6 (2–23)	**0.017**	19 (2–57)	6 (6)	0.526
CVC at index culture, *n* (%)	12 (48.0)	29 (48.3)	0.978	31 (48.4)	10 (47.6)	0.948
Mean days of CVC until index culture ± SD (range)	21.17 ± 16.53 (4–53)	16.80 ± 15.69 (0–73)	0.371	19.56 ± 17.46 (0–73)	13.20 ± 7.76 (6–30)	0.475
Urinary catheter at index culture, *n* (%)	14 (56.0)	52 (86.7)	**0.002**	48 (75.0)	18 (85.7)	0.306
Days of urinary catheter until index culture, median (range)	34 (3–100)	17 (1–214)	0.055	24 (1–214)	17 (1–52)	0.391
Candiduria at index culture, *n* (%)	4 (16.0)	20 (33.3)	0.106	17 (26.6)	7 (33.3)	0.550
Polymicrobial bacteremia/fungemia, *n* (%)	8 (32.0)	8(13.3)	**0.045**	15 (23.4)	1 (4.8)	0.057
Antifungal therapy prior to index culture, *n* (%)	11 (44.0)	9 (15.0)	**0.004**	20 (31.2)	0 (0.0)	**0.003**
Antifungal prophylaxis within 30 days, *n* (%)	16 (64.0)	12 (20.0)	**< 0.001**	27 (42.2)	1 (4.8)	**0.002**
Antibacterial therapy, *n* (%)	22 (88.0)	58 (96.7)	0.122	60 (93.7)	20 (95.2)	0.801
Days of antibacterial therapy until index culture, median (range)	18 (1–71)	15 (1–64)	0.058	17 (1–71)	14 (1–46)	0.129
Parenteral nutrition, *n* (%)	12 (48.0)	47 (78.3)	**0.006**	44 (68.8)	15 (71.4)	0.817
Breakthrough fungemia	9 (36)	9 (15)	**0.031**	18 (28.1)	0 (0.0)	**0.003**
Mortality, *n* (%)			0.774			0.716
• 10-day	13 (52)	31 (51.6)		38 (59.4)	8 (38.1)	
• 30-day	18 (72.0)	45 (75.0)		48 (75.0)	15 (71.4)	

[a]*P*-values ≤ 0.05 are expressed in bold;
[b]the source of statistical difference was only hematology/onchology wards;
[c]the source of statistical difference was only hematological malignancies; ICU, intensive care unit.

of *R. mucilaginosa* isolates, fluconazole MIC values were ≥ 32 μg/ml.[6,12,14] Similarly, relatively high fluconazole MICs have also been reported for other NCYs in the literature: 0.25–32 μg/ml for *T. asahii*, 1–128 μg/ml for *M. capitatus*, 0.25–48 μg/ml for *S. cerevisiae*.[6,8,12,14]

Consistent with the findings of previous studies, the MIC values of voriconazole and posaconazole were low among *T. asahii* and *C. dermatis* isolates; voriconazole MIC values for *T. asahii*, *M. capitatus, R. mucilaginosa*, and *S. cerevisiae* isolates have been reported as ≤ 0.125 μg/ml, ≤ 4.0 μg/ml, ≤

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4.0 μg/ml, and ≤ 1.0 μg/ml, respectively.[9,12,14] Unfortunately, fluconazole-resistant isolates of NCYs may also exhibit decreased susceptibility to voriconazole, as observed in *Candida* spp.[13]

Except for the isolates of one *C. dermatis* and one *S. cerevisiae*, the MIC values for caspofungin and anidulafungin were high against all isolates, particularly among *M. capitatus, M. clavatus, T. asahii,* and *R. mucilaginosa* isolates, in line with previous reports.[6,7,12] Previously, *Geotrichum, Rhodotorula, Magnusiomyces*, and *Trichosporon* have been reported to be intrinsic resistant or non-susceptible to echinocandins.[2,5,13–15]

MIC range of amphotericin B was 0.25–2 μg/ml for our NCY isolates; MIC = 2 μg/ml for one *R. mucilaginosa* and one *G. candidum*, MIC ≤ 1 μg/ml for others. Although MIC values of amphotericin B against the isolates of *M. capitatus, R. mucilaginosa* and *S. cerevisiae* have been reported to be ≤ 2 μg/ml, *T. asahii* isolates had a MIC range of ≤ 0.5–≥ 8 μg/ml, *in vitro*.[6,9,12,14] Although relatively low amphotericin B MICs were obtained for *T. asahii* isolates in the present study, it has been reported highly resistant to amphotericin B, in addition to fluconazole and echinocandins.[8,13]

Both previous reports and our *in vitro* results show that fluconazole and echinocandins are not good choices for NCY isolates, and there is no a single antifungal drug that will be effective against all isolates tested. Liposomal amphotericin B with/without flucytosine is recommended (moderately) in systemic first-line antifungal therapy for *Magnusiomyces* spp., *Rhodotorula* spp., *Saccharomyces* spp., and *Geotrichum* spp. in the global guideline for the diagnosis and management of rare yeast infections.[2] First-line therapy drugs for *Trichosporon* spp. infections are voriconazole or posaconazole in this guideline (moderately recommended). In addition, echinocandins for species of *Magnusiomyces, Trichosporon, Geotrichum*, and echinocandins and triazoles for *Rhodotorula* species were the drugs recommended to be avoided.[2] This emphasizes the importance of species identification and antifungal susceptibility testing in the management of NCY fungemia.

The epidemiology of yeast infections is changing over time, and non-*albicans Candida* species and NCY have emerged as important opportunistic pathogens. NCY, less common than *Candida*, has been associated with life-threatening infections in immunocompromised hosts or severely ill patients. The most common underlying conditions or predisposing factors associated with the invasive infection due to NCY have been reported as hematological malignancies, neutropenia, ICU stay, presence of CVC, and TPN.[4,7,9,15] However, NCY fungemia episodes were discussed alone in these studies, and they did not include any comparison for these risk factors according to all fungemia episodes. Fernandez-Ruiz et al.[6] compared the BSI due to uncommon yeasts (non-*Candida*, non-*Cryptococcus*) with those due to *Candida* species in 29 Spanish hospitals and reported that the patients with fungemia due to rare yeasts ($n = 14$) were more likely to have hematological malignancy, immunosuppressive therapy, and neutropenia. For our patients, hematological malignancy, immunosuppressive therapy, and neutropenia, as well as admission to hematology/oncology wards, prolonged neutropenia, polymicrobial bacteremia/fungemia, preexposure to antifungal drugs, and breakthrough fungemia were more frequently associated with NCY fungemia compared to candidemia. Furthermore, we observed that ICU admission, diabetes mellitus, urinary catheters, and TPN were associated with candidemia rather than NCY fungemia. A multicenter, prospective, case-control study in France reported that diabetes mellitus, presence of CVC, and urinary catheter, TPN was independent risk factors associated with candidemia.[16] Although it was statistically insignificant, the presence of CVC and TPN were more common in candidemia patients (64% vs 78% and 29% vs 49%, respectively) in the previous study comparing fungemia due to *Candida* and NCY.[6]

Bretagne et al.[12] compared the candidemia due to *C. albicans* and fungemia due to uncommon yeast species (UYS), including non-*albicans Candida* and non-*Candida* yeasts; hematological malignancies and preexposure to antifungal drugs were significantly associated with UYS fungemia, whereas solid tumors were associated with *C. albicans* fungemia. Similar to these results, we observed that the chemotherapy, neutropenia, preexposure to antifungal drugs, and breakthrough fungemia were significantly associated with fungemia other than candidemia caused by *C. albicans*; the candidemia caused by *C. albicans* did not involve chemotherapy, neutropenia, preexposure to antifungal drugs, or breakthrough fungemia in our study. The fact that many of these rare yeasts, including several non-*albicans Candida* species have intrinsic or variable resistance to antifungals may explain the occurrence of breakthrough infections in patients receiving empiric antifungal therapy in hematology/oncology wards and the patients with hematological malignancy.

In summary, when all fungemia episodes were considered in this study, chemotherapy, neutropenia, and preexposure to antifungal drugs were risk factors for all fungemia caused by yeasts except *C. albicans*. Hospitalization in hematology/oncology wards, hematological malignancies, immunosuppressive therapy (any), prolonged neutropenia, and polymicrobial bacteremia/fungemia were additional risk factors for NCY fungemia. ICU admission, diabetes mellitus, urinary catheters, and TPN were risk factors for candidemia. It was observed that old age, prolonged hospitalization, the presence of CVC, and a high frequency of antibacterial treatment were risk factors for all fungemia (candidemia, non-*Candida* fungemia, or *C. albicans* fungemia) episodes, and high mortality rates were associated with all fungemia episodes in our study.

In conclusion, the growing problem of fungemia reflects the increasing number of patients at risk. The present results show that the majority of fungemia due to non-*Candida* yeast species is the problem, particularly for hematology units and patients with the hematological malignancy in our center. Preexposure to antifungal drugs causes a change in the epidemiology of fungemia in favor of non-*albicans Candida* and/or NCY, resulting breakthrough fungemia. It has been seen that diabetes mellitus, urinary catheterization, and TPN are the more significant predisposing factors for candidemia in this study. The increasing frequency of immunocompromised hosts may be an indicator that the incidence of NCY infections will increase in the next years. Early identification and antifungal susceptibility testing of the agent, increased communication among physicians and laboratories are important in the management of fungemia due to NCY because they have variable antifungal susceptibility characteristics.

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Author contributions

Yasemin Oz (Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing), Mustafa Yılmaz (Data curation, Investigation, Methodology, Writing – review & editing), Tuba Bulduk (Data curation, Investigation, Methodology, Writing – review & editing), Mehmet Basayigit (Data curation, Investigation, Methodology, Writing – review & editing), Eren Gunduz (Data curation, Investigation, Methodology, Writing – review & editing), and Selma Metintas (Methodology, Supervision, Validation, Writing – review & editing)

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Conflict of interest

The authors declare that there are no conflict of interest.

References

1. Mizusawa M, Carroll KC. Updates on the profile of GenMark's ePlex blood culture identification fungal pathogen panel. *Expert Rev Mol Diagn*. 2023; 23(6): 475–484.
2. Chen SC, Perfect J, Colombo AL et al. Global guideline for the diagnosis and management of rare yeast infections: an initiative of the ECMM in cooperation with ISHAM and ASM. *Lancet Infect Dis*.2021; 21(12): e375–e386.
3. Lohmann C, Sabou M, Moussaoui W et al. Comparison between the Biflex III-Biotyper and the Axima-SARAMIS systems for yeast identification by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *J Clin Microbiol*. 2013; 51(4): 1231–1236.
4. Arendrup MC, Boekhout T, Akova M et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. *Clin Microbiol Infect*. 2014; 20(Suppl 3): 76–98.
5. Lin SY, Lu PL, Tan BH et al. The epidemiology of non-*Candida* yeast isolated from blood: the Asia Surveillance Study. *Mycoses*.2019; 62(2): 112–120.
6. Fernández-Ruiz M, Guinea J, Puig-Asensio M et al. CANDIPOP Project; GEIH-GEMICOMED (SEIMC) and REIPI. Fungemia due to rare opportunistic yeasts: data from a population-based surveillance in Spain. *Med Mycol*. 2017; 55(2): 125–136.
7. Chitasombat MN, Kofteridis DP, Jiang Y et al. Rare opportunistic (non-*Candida*, non-*Cryptococcus*) yeast bloodstream infections in patients with cancer. *J Infect*. 2012; 64(1): 68–75.
8. Yamamoto M, Takakura S, Hotta G et al. Clinical characteristics and risk factors of non-*Candida* fungaemia. *BMC Infect Dis*.2013; 13: 247.
9. Alp S, Gulmez D, Ayaz CM, Arikan-Akdagli S, Akova M. Fungaemia due to rare yeasts in a tertiary care university centre within 18 years. *Mycoses*.2020; 63(5): 488–493.
10. CLSI. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard—Third Edition. CLSI document M27-A3*. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.
11. CLSI. Performance standards for antifungal susceptibility testing of yeasts. 2nd edn. *CLSI Supplement M60*. Wayne, PA: Clinical and Laboratory Standards Institute; 2020.
12. Bretagne S, Renaudat C, Desnos-Ollivier M et al. French Mycosis Study Group. Predisposing factors and outcome of uncommon yeast species-related fungaemia based on an exhaustive surveillance programme (2002-14). *J Antimicrob Chemother*. 2017; 72(6): 1784–1793.
13. Pfaller MA, Diekema DJ, Gibbs DL et al. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: 10.5-year analysis of susceptibilities of noncandidal yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. *J Clin Microbiol*. 2009; 47(4): 117–123.
14. Spiliopoulou A, Lekkou A, Vrioni G et al. Fungemia due to rare non-Candida yeasts between 2018 and 2021 in a Greek tertiary care university hospital. *J Mycol Med*. 2023; 33(3): 101386.
15. Noster J, Koeppel MB, Desnos-Olivier M et al. Bloodstream infections caused by *Magnusiomyces capitatus* and *Magnusiomyces clavatus*: epidemiological, clinical, and microbiological features of two emerging yeast species. *Antimicrob Agents Chemother*.2022; 66(2): e0183421.
16. Poissy J, Damonti L, Bignon A et al. Risk factors for candidemia: a prospective matched case-control study. *Crit Care*. 2020; 24(1): 109.

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