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Case Report

A Retrospective Study on the Prevalence and *In Vitro* Antifungal Susceptibility among Isolates from Invasive Candidiasis in Saudi Arabia

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Abstract

Background: Invasive candidiasis (IC) is a progressive and potentially fatal infection. Five *Candida* species (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei*) typically account for most IC cases, but their relative frequencies can vary to institutional level.

Methods: This retrospective observational study aimed to analyze the species distribution and antifungal susceptibility of *Candida* isolates from confirmed IC cases, determined according to the local criteria, at four participating hospitals in three major regions of Saudi Arabia. The study reviewed laboratory records for all IC cases, confirmed by positive culture of a *Candida* species as part of routine specimen analysis. Data included isolate identification, determined using standard methodologies, and antifungal susceptibility, according to published breakpoints.

Results: Among a total of 1,095 isolates, *C. albicans* was the most common (28.8%), followed by *C. parapsilosis* (17.5%), *C. tropicalis* (17.2%), *C. glabrata* (15.1%) and *C. auris* (8.9%). *C. albicans* showed high susceptibility of > 87%. *C. albicans, C. parapsilosis* and *C. tropicalis* exhibited high susceptibility to caspofungin, micafungin and amphotericin B (≥ 98.5%). *C. glabrata* showed high susceptibility of ≥ 86.4% to voriconazole, micafungin, flucytosine, and amphotericin B. The susceptibility of *C. dubliniensis* to all agents was 51.9%–75.0%. The rate of multidrug resistance among *C. auris* isolates was 33.7%.

Conclusions: These results provide real-world insights into the distribution of *Candida* species, and antifungal susceptibility, resistance patterns, and resistance phenotypes. This information is valuable for understanding the local epidemiology of IC and guiding appropriate treatment strategies to aid in improving patient care.

Keywords: Invasive candidiasis; Infection; *Candida* species; Saudi Arabia; Antifungal resistance; Antifungal susceptibility.

Abbreviations

CDC: Centers for Disease Control and Prevention; CLSI: Clinical and Laboratory Standards Institute; IC: Invasive Candidiasis; ICU: Intensive Care Unit; KAMC-J: King Abdulaziz Medical City, Jeddah; KFSH-D: King Fahad Specialist Hospital, Dammam; KFSH&RC-J: King Faisal Specialist Hospital and Research Center, Jeddah; KSMC-R: King Saud Medical City Hospital, Riyadh; MIC: Minimum Inhibitory Concentration; MDR: Multidrug-resistant; R: Resistant; S: Susceptible; XDR: Extensively Drug-resistant; Y: Years.

Introduction

Invasive candidiasis (IC) is a severe and potentially life-threatening infection that includes candidemia (bloodstream infections) and deep-seated tissue candidiasis (following dissemination to other body sites) [1]. Studies using global patient data have reported mortality rates for nosocomial candidemia and IC that exceed 30% [2-5]. IC is most commonly observed among patients in the intensive care unit (ICU) and only around 10% of IC cases occur in the community [6].

Candidiasis is often opportunistic and reportedly, five *Candida* species account for more than 90% of diagnosed cases: *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* [7,8]. Their relative frequencies will vary by geographical location, even within the same region and country, and may vary according to clinical setting and practice [7].

Globally, more than 700,000 cases of IC are reported annually [6] and in Saudi Arabia, reported IC rates were 1.55 and 1.65 cases per 1,000 hospital discharges or admission, and 2.6 cases per 100 ICU admissions [9–11]. The rate of candidemia in Saudi Arabia ranged between 0.2 and 0.76 cases per 1,000 hospital discharges [12]. The causative pathogen in the majority of candidemia cases is *C. albicans*, although its incidence is declining globally [8]. By contrast, the isolation of *C. glabrata*, which is associated with increasing patient age, is increasing [7,8].

C. glabrata has been designated as a "critical threat" fungal

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pathogen by the World Health Organization [13], along with *C. auris*, a highly transmissible emerging pathogen which is increasingly being reported and now identified in 47 countries [14]. Among a global collection of *C. auris* isolates, 23% were multidrug-resistant (MDR), 80% were resistant to fluconazole, a commonly used antifungal agent, and resistance was also demonstrated to other first-line agents among the echinocandins and polyenes [15].

The objective of this retrospective study was to determine the most common *Candida* species causing IC and their antifungal susceptibility to help to improve patient care.

Methods

Study Design

This retrospective observational study aimed to analyze the species distribution and antifungal susceptibility of isolates from confirmed IC cases at four participating hospitals from three of the major regions in Saudi Arabia.

Data Collection

The study included all clinical isolates of *Candida* species that were determined by local criteria to cause IC. Data were collected from the laboratory records of adult and pediatric patients from the following hospitals in Saudi Arabia: King Abdulaziz Medical City, Jeddah (KAMC-J); King Fahad Specialist Hospital, Dammam (KFSH-D); King Faisal Specialist Hospital and Research Center, Jeddah (KFSH&RC-J); and King Saud Medical City Hospital, Riyadh (KSMC-R). The records were reviewed for all cases of IC confirmed by positive culture of a *Candida* species, as a part of routine specimen analysis. Demographic information on the submitted isolates from confirmed IC cases are presented in Supplementary Table 1.

Data were collected for qualifying isolates of *Candida* species that were tested between January 2017 and December 2022. The collected data included species identification, minimum inhibitory concentration (MIC) data or categorical antifungal susceptibility, source of isolate, patient age and sex, and ward type. The isolates were obtained from both adult and pediatric patients and were limited to confirmed IC.

Isolation and Identification of *Candida* Species

The routine isolation and identification of *Candida* species was conducted using local standard methodologies. Isolates obtained from direct plating of specimens on solid media, or from positive blood culture bottles, were identified using classical morphological and biochemical tests, or automated systems, such as Vitek® MS or Vitek® 2 (bioMerieux, Marcy-l'Etoile, France).

Antifungal Susceptibility Testing

The identified isolates were tested locally for their susceptibility to a range of antifungal agents using the Vitek® 2 or Sensititre™ YeastOne™ systems (Thermo Fisher Scientific, Waltham, MA USA). KAMC-J provided MIC data, and KFSH-D, KFSHRC-J and KSMC-R provided categorical antifungal susceptibility data. The MIC results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints available at the time of testing [16]. For *C. auris*, which lacks established CLSI breakpoints, the study applied tentative MIC breakpoints proposed by the United States Centers for Disease Control and Prevention (CDC) [17]. These included MIC thresholds of resistance for fluconazole (≥ 32 µg/mL), amphotericin B (≥ 2 µg/mL), caspofungin (≥ 2 µg/mL), and micafungin (≥ 4 µg/mL). In the absence of CDC tentative breakpoints for other triazoles, the CLSI epidemiological cutoff value for voriconazole against *C. glabrata* (≥ 0.25 µg/mL) was used [18].

Table 1: Rates of antifungal susceptibility among 7 main Candida species collected from confirmed invasive candidiasis cases, overall and from adult (≥ 18 years) and pediatric (0–17 years) patients, between 2017 and 2022 from four hospitals in Saudi Arabia.

Species	Fluconazole		Voriconazole		Caspofungin		Micafungin		Amphotericin B		Flucytosine	
	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S
Overall (N = 1,095[a])												
C. albicans	323	92.6	300	95.3	322	99.4	296	100	265	99.2	180	87.8
C. parapsilosis	194	83.0	187	87.2	195	98.5	188	99.5	151	98.7	128	85.9
C. tropicalis	194	84.0	168	91.7	194	98.5	167	99.4	146	100	82	84.1
C. glabrata	140	47.1	81	86.4	146	74.0	145	89.0	108	99.1	65	89.2
C. auris	98	11.2[b]	97	86.6[b]	98	94.9[b]	96	99.0[b]	97	87.6[b]	97	95.9[b]
C. dubliniensis[c]	27	51.9	27	59.3	26	61.5	26	61.5	27	63.0	16	75.0
C. krusei	26	0.0[d]	29	93.1	30	56.7	31	100	23	91.3	4	--
Adult patients (n = 881)												
C. albicans	230	90.9	206	93.7	229	99.1	204	100	177	98.9	108	84.3
C. parapsilosis	152	80.9	145	85.5	152	98.7	145	100	110	99.1	94	81.9
C. tropicalis	154	83.8	128	90.6	154	98.1	127	99.2	110	100	55	85.5
C. glabrata	130	46.9	71	85.9	135	72.6	134	88.8	98	99.0	55	89.1
C. auris	95	11.6[b]	94	88.3[b]	95	95.8[b]	93	98.9[b]	94	88.3[b]	94	95.7[b]
C. dubliniensis[c]	24	54.2	24	62.5	23	65.2	23	65.2	24	62.5	15	73.3
C. krusei	23	0.0[d]	26	92.3	27	59.3	28	100	20	95.0	3	--
Pediatric patients (n = 209)												
C. albicans	89	96.6	90	98.9	89	100	88	100	84	100	68	92.6
C. parapsilosis	42	90.5	42	92.9	43	97.7	43	97.7	41	97.6	34	97.1
C. tropicalis	39	84.6	39	94.9	39	100	39	100	35	100	27	81.5

Abbreviations: CDC, Centers for Disease Control and Prevention; CLSI, Clinical and Laboratory Standards Institute; and S, susceptible.
--, %S values not shown for species with < 10 isolates and isolates were not all tested against each antifungal agent by each hospital.
[a]Five patients with missing age data are not included.
[b]No CLSI breakpoints available for *C. auris*. CDC tentative resistance breakpoints or CLSI epidemiological cutoff value were applied, as appropriate, and values shown are for % non-resistant isolates.
[c]*C. dubliniensis* was identified at KAMC-J, KFSH-D, and KSMC-R.
[d]*C. krusei* is intrinsically resistant to fluconazole.

Ethical Approval

Local institutional review board approval was obtained for each participating hospital before initiating data collection. Patient consent was not required.

Data Analysis

Statistical Analysis: The data collected from the four participating hospitals were collated and analyzed using SAS version 9.4 (Cary, NC, USA) by Micron Research Ltd (Ely, Cambridgeshire, UK) to determine the local epidemiology of IC.

Species Distribution: The distribution of *Candida* species was determined overall and by hospital. The proportions of each species identified were calculated to provide the prevalence of different *Candida* species in confirmed IC cases.

Antifungal Susceptibility: The susceptibility of *Candida* isolates to commonly used antifungal agents (fluconazole, voriconazole, caspofungin, micafungin, amphotericin B, and flucytosine) at the four participating hospitals was analyzed. Susceptibility data were calculated overall, and stratified by patient age groups and by year, for *C. albicans*, *C. auris*, *C. dubliniensis*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*. Three hospital laboratories (KFSH-D, KFSH&RC-J, and KSMC-R) submitted categorical susceptibility data. KAMC-J submitted MIC data, which were interpreted as described above (see 'Antifungal susceptibility testing') to determine susceptibility categories.

Resistance Patterns: The percentages of isolates from each species that were azole-resistant, echinocandin-resistant, MDR, and extensively drug-resistant (XDR) were calculated. MDR was defined as nonsusceptibility of an isolate to at least one agent in two or more drug classes, while XDR was defined as nonsusceptibility to at least one agent in three or more drug classes, except for *C. auris*, when MDR and XDR were based on numbers of resistant isolates (not non-susceptible). This analysis provided insights into the resistance patterns of different *Candida* species in the local IC population.

Cross-resistance: The analysis also determined cross-resistance between antifungal agents for all species. The Spearman Rank correlation test was used to assess the correlation between MIC values of different antifungal agents. A correlation coefficient (r) of ≥ 0.6 indicated cross-resistance and was used to identify potential patterns of cross-resistance between antifungal agents.

Results

Distribution of Isolates

A total of 1,095 *Candida* isolates were included in the study between 2017 and 2022. Supplementary Table 1 presents the collected demographic data on source of isolate, patient age and sex, and ward type. Overall, the most common species identified was *C. albicans* (28.8%), followed by similar numbers of *C. parapsilosis* (17.5%) and *C. tropicalis* (17.2%), and *C. glabrata* (15.1%) (Figure 1). *C. auris* comprised 8.9% of isolates, surpassing *C. krusei* and *C. dubliniensis* (each 3.1%) (Figure 1).

The number of *Candida* isolates collected by each hospital and the years of data collection were: KAMC-J, 201 (2020–2022); KFSH-D, 233 (2017–2021); KFSH&RC-J, 79 (2018–2022); and KSMC-R, 582 (2017–2021). The distribution of species varied across the four hospitals, with different rates of each species observed (Figure 2). KAMC-J had the lowest rate of *C. albicans* (17.4%) and *C. tropicalis* (10.4%) isolates and the highest rate of *C. auris* (22.4%). By contrast, KFSH-D had the highest rate of *C. albicans* (33.9%) but no *C. auris* isolates. KFSH&RC-J had the highest rates of *C. tropicalis* (32.9%) and *C. glabrata* (24.1%), and the lowest rate of *C. parapsilosis* (7.6%). KSMC-R had the highest rate of *C. parapsilosis* (22.0%) and lowest *C. glabrata* rate (11.2%).

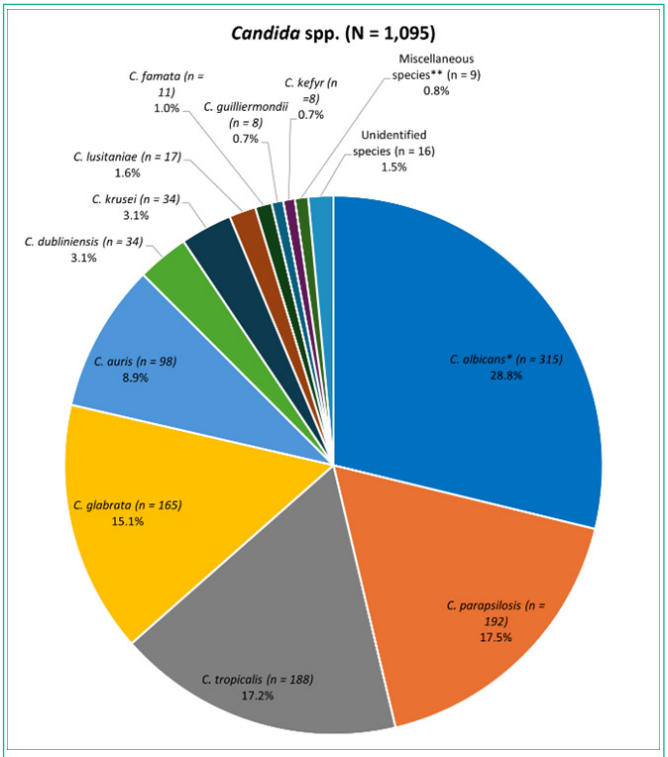

Figure 1: Overall distribution of all *Candida* species collected from confirmed invasive candidiasis cases between 2017 and 2022 from four hospitals in Saudi Arabia.
*Includes one isolate from KFSH&RC-J identified as *C. albicans*/*C. glabrata*.
**Comprises *C. ciferrii* (n = 3), *C. utilis* (n = 2), *C. haemulonii* (n = 1), *C. lipolytica* (n = 1), *C. orthopsilosis* (n = 1) and *C. rugosa* (n = 1).

Antifungal Susceptibility

Overall, *C. albicans* showed high susceptibility rates of > 87% to all agents (Table 1). *C. parapsilosis* and *C. tropicalis* also exhibited high susceptibility to caspofungin, micafungin and amphotericin B (≥ 98.5%), with rates of 83.0%–91.7% to the remaining agents. Comparing the agents, the highest susceptibility of *C. glabrata* was to amphotericin B (99.1%), followed by voriconazole, micafungin and flucytosine (86.4%–89.2%), with lower susceptibility to caspofungin (74.0%) and fluconazole (47.1%). Approximately 89% of *C. auris* was resistant to fluconazole but less than 14% of isolates were resistant to the other agents.

C. krusei is intrinsically resistant to fluconazole but susceptible to voriconazole, micafungin, and amphotericin B (91.3%–100%), with lower susceptibility to caspofungin (56.7%) (Table 1). *C. dubliniensis* showed lower susceptibility to all agents (51.9%–75.0%).

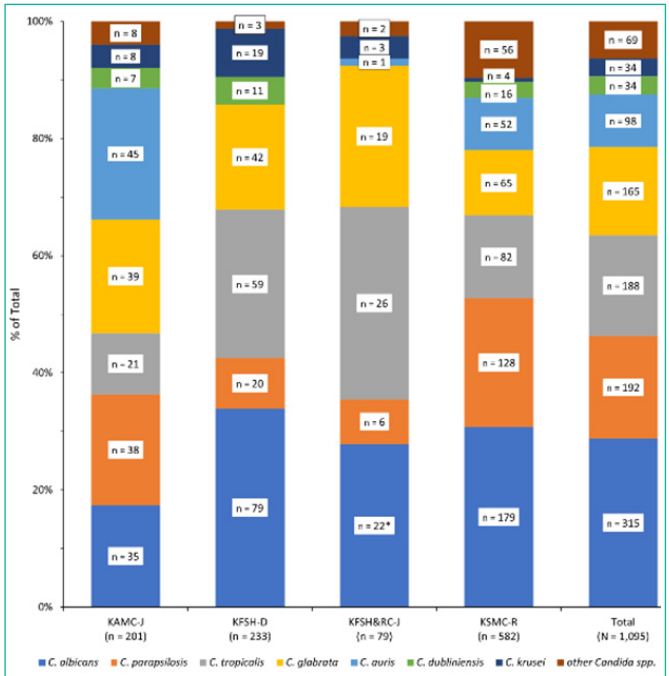

Figure 2: Distribution of *Candida* species collected from confirmed invasive candidiasis cases between 2017 and 2022 from four hospitals in Saudi Arabia, by hospital.
Abbreviations: KAMC-J, King Abdulaziz Medical City, Jeddah; KFSH-D, King Fahad Specialist Hospital, Dammam; KFSH&RC-J, King Faisal Specialist Hospital and Research Center, Jeddah; and KSMC-R, King Saud Medical City Hospital, Riyadh.
*Includes one isolate from KFSH&RC-J identified as *C. albicans*/*C. glabrata*.

The pattern of antifungal susceptibility of isolates from adult patients was similar to the overall collection (Table 1). For the pediatric patients, data were available for three *Candida* species (*C. albicans*, *C. parapsilosis* and *C. tropicalis*) (Table 1). More than 90% of *C. albicans* and *C. parapsilosis* from pediatric patients were susceptible to all six tested agents, whereas *C. tropicalis* showed lower susceptibility to fluconazole (84.6%) and flucytosine (81.5%), and higher susceptibility to the other four agents (94.9%–100%).

Susceptibility Trends

There was a decreasing trend in susceptibility to the azoles over the study period, and to flucytosine between 2017 and 2020 (Figure 3). Micafungin and amphotericin B remained active over the years; however, *C. glabrata* susceptibility to micafungin decreased during the study period. Moreover, comparing the species, *C. glabrata* showed the most pronounced changes, remaining >90% susceptible only to amphotericin B throughout the study period.

Resistance Phenotypes

Azole resistance was low (< 15%) for all named species except *C. auris*, *C. krusei* and *C. famata* (> 53%) (Table 2). Echinocandin resistance rates were also low, with the highest rate observed for *C. krusei* (8.8%). MDR rates were highest for *C. auris*, *C. dubliniensis*, *C. krusei*, and *C. famata* (29.4%–36.4%), followed by *C. glabrata* and *C. lusitaniae* (12.5%–17.5%). For species with ≥ 10 isolates, less than 4.7% of the remaining species were MDR. XDR isolates were most common for *C. dubliniensis* (26.5%), with lower rates for the other species with ≥ 10 isolates (≤ 6.3%).

Table 2: Rates of resistance phenotypes among *Candida* species collected from confirmed invasive candidiasis cases between 2017 and 2022 from four hospitals in Saudi Arabia.

Species	Azole-R		Echinocandin-R		MDR		XDR	
	n	%	n	%	n	%	n	%
C. albicans, n = 321	18	5.6	0	0.0	9	2.8	0	0.0
C. parapsilosis, n = 195	26	13.3	0	0.0	6	3.1	1	0.5
C. tropicalis, n = 193	21	10.9	1	0.5	9	4.7	0	0.0
C. glabrata, n = 166	15	9.0	7	4.2	29	17.5	1	0.6
C. auris, n = 98	87	88.8	5	5.1	33	33.7[a]	5	5.1[a]
C. dubliniensis, n = 34[b]	2	5.9	0	0.0	12	35.3	9	26.5
C. krusei, n = 34	34	100[c]	3	8.8	10	29.4	1	2.9
C. lusitaniae, n = 16	2	12.5	0	0.0	2	12.5	1	6.3
C. famata, n = 11	6	54.6	0	0.0	4	36.4	0	0.0
C. guilliermondii, n = 8	1	12.5	0	0.0	1	12.5	0	0.0
C. kefyr, n = 8	0	0.0	0	0.0	2	25.0	1	12.5
C. ciferrii, n = 3	3	100	0	0.0	1	33.3	0	0.0
C. haemulonii, n = 1	0	0.0	0	0.0	1	100	1	100
C. lipolytica, n = 1	0	0.0	0	0.0	1	100	0	0.0
Candida spp., n = 15	4	26.7	2	13.3	2	13.3	1	6.7

Abbreviations: MDR, multidrug-resistant; R, resistant; and XDR, extensively drug-resistant.
MDR defined as non-susceptible to ≥ 1 agent in ≥ 2 drug classes and XDR defined as non-susceptible to ≥ 1 agent in ≥ 3 drug classes (XDR isolates are included in the MDR counts); except for [a]*C. auris*, when MDR and XDR were based on numbers of resistant isolates (not non-susceptible).
[b]*C. dubliniensis* was identified at KAMC-J, KFSH-D, and KSMC-R.
[c]*C. krusei* is intrinsically resistant to fluconazole.

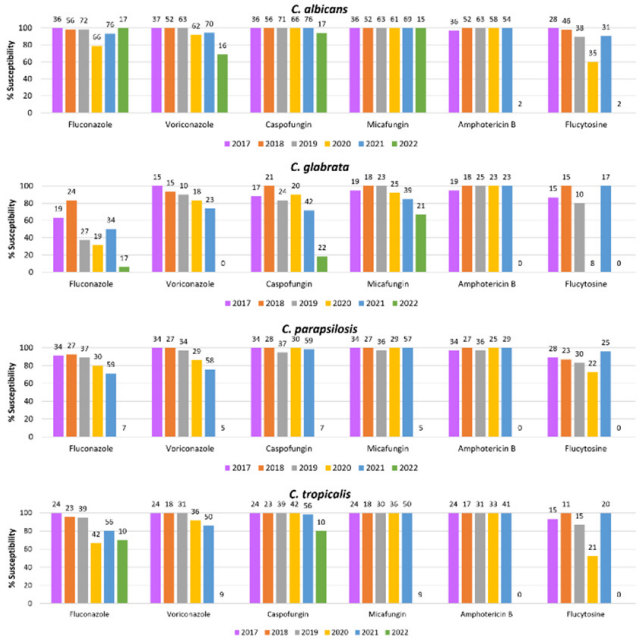

Figure 3: Rates of antifungal susceptibility of 4 main *Candida* species collected from confirmed invasive candidiasis cases between 2017 and 2022 from four hospitals in Saudi Arabia, by year.
Total number of isolates tested shown above each column.
% S values not shown for species with < 10 isolates.

Cross-resistance

Positive correlations (r ≥ 0.6) were observed between several pairs of antifungal agents for different species, indicating cross-resistance. Examples of positively correlated pairs for *C. albicans* were voriconazole and caspofungin (r = 0.73), voriconazole and micafungin (r = 0.82), caspofungin and micafungin (r = 0.82), caspofungin and flucytosine (r = 0.69), and micafungin and flucytosine (r = 0.63). Positive correlations were also observed for *C. auris* (fluconazole and voriconazole [r = 0.65]), for *C. glabrata* (micafungin and flucytosine

[r = 0.79]), and for *C. tropicalis* (caspofungin and micafungin [r = 0.73]; and micafungin and flucytosine [r = 0.65]).

Discussion

This study of *Candida* isolates from four hospitals in three of the major regions of Saudi Arabia aimed to investigate the prevalence of different *Candida* species causing IC between 2017 and 2022, and the susceptibilities of isolates to a panel of antifungal agents.

Overall, *C. albicans* accounted for approximately 30% of the isolates, followed by *C. parapsilosis*, *C. tropicalis* and *C. glabrata*, which occurred at similar rates (15.1%–17.5%). These four most common species are consistent with previous hospital studies conducted in Saudi Arabia; however, the reported order and frequencies of each species varied between the hospitals [9,11,19–25,27,28]. For example, the overall prevalence of *C. albicans* at KSMC-R (30.8%) was slightly lower than other data from Riyadh (38.3%–50.3%) [9,11,25,26], but higher in KFSH-D (33.9%) compared with published data from Dammam (18.8%) [**27**]. *C. glabrata* was found to be the most prevalent species in two studies [**27,28**], and over a 10-year period in Saudi Arabia, *C. glabrata*, as causative pathogen of IC, showed a 10-fold increase ($P < 0.001$) while *C. albicans* remained fairly stable [**9**]. In our study, *C. glabrata* exceeded *C. parapsilosis* at all hospitals except KSMC-R.

A notable finding in the current study was the emergence of *C. auris,* which accounted for 8.9% of the total isolates, and replaced *C. krusei* as one of the five most commonly reported species causing candidiasis [7,8]. *C. dubliniensis*, which showed the lowest susceptibility of all the species presented, was identified at low levels (< 5%) at three of the four hospitals.

Regarding antifungal susceptibility, fluconazole showed the lowest activity against *Candida* species, while micafungin demonstrated the highest activity, followed by caspofungin and amphotericin B. *C. albicans* exhibited the highest rates of susceptibility among the seven main *Candida* species identified, among which, *C. dubliniensis* tended to display the lowest antifungal susceptibility. Echinocandin resistance remained uncommon among all species. According to the clinical practice guidelines for the management of IC in the Middle East region, echinocandins are preferred for the treatment of proven and suspected *Candida* infections, particularly for *C. glabrata* or *C. krusei*, and in critically ill patients or those with previous exposure to azoles [**20**].

C. dubliniensis showed a low rate of azole resistance (5.9%) and no echinocandin resistance, while multidrug resistance rates above 29% were observed in *C. auris*, *C. dubliniensis*, *C. krusei* and *C. famata*. The rates of multidrug resistance remained low (< 5%) among *C. albicans*, *C. parapsilosis*, and *C. tropicalis*. Of concern was that 33.7% of *C. auris* isolates were MDR and 88.8% were azole-resistant. The management of *C. auris* poses a challenge and there are currently no specific guidelines for managing this species in our region [20]. The US CDC recommends the use of echinocandins, although antifungal resistance to these agents is increasing [29].

Cross-resistance between antifungal agents in the current study was observed most frequently for the echinocandins in *C. albicans*, as has been discussed in the literature but not by other studies from Saudi Arabia [27,28,30], although previous echinocandin exposure was associated with antifungal resistance ($P = 0.006$) in a candidemia study from Jeddah where *C. glabrata* was the dominant species [28]. In the current study, *C. tropicalis* exhibited cross-resistance between both echinocandins and flucytosine, while cross-resistance in *C. auris* was limited to the azoles.

This was a valuable study, with real-world findings on the distribution of *Candida* species, their antifungal susceptibility, trends over time, resistance phenotypes, and cross-resistance patterns. It provided important data, despite certain limitations, such as the retrospective study design, small number of participating hospitals, and varied total isolate numbers collected by each hospital. Further research could include the molecular characterization of *Candida* isolates to provide information on resistance mechanisms, and the continued monitoring of epidemiology to determine factors associated with species distribution and antifungal susceptibility.

In conclusion, this study highlighted the wide variation in the distribution of *Candida* species causing IC in Saudi Arabia and the rates of resistance phenotypes. Our findings emphasize the importance of considering hospital-specific epidemiology when managing this condition.

Transparency Declarations

Ashraf Hassanien, Naglaa Mohamed are current employees of Pfizer and Eric Utt is a former Pfizer employee. The remaining authors have none to declare.

Author Contributions

Abdulfattah Al-Amri, Mona Al-Dabbagh, Raed Al-Hababi, Yamama Aljishi, Basem Alraddadi, Omar Alzomor, Manal Atta and Mohammed Qutub participated in data collection. All authors were involved in data interpretation, drafting and reviewing the manuscript, and approved the final manuscript.

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