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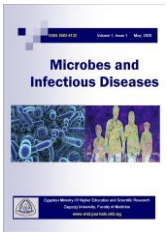

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Original article

Species distribution and antifungal susceptibility patterns of *Candida* isolated from critically ill patients with candidemia

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ABSTRACT

Background: Candidemia, the prevailing form of invasive candidiasis, is a serious medical condition with high fatality rates particularly among individuals who are critically ill. We conducted this study to investigate the distribution of *Candida* species and their susceptibility to different antifungal drugs among patients with candidemia in intensive care units. **Methods:** For one year, seventy-four *Candida* isolates were obtained from the blood of pediatric and adult patients in intensive care units of Kasr Alainy University Hospitals. The Vitek-2 yeast identification system was employed to identify the isolates. Additionally, the antifungal susceptibility of all isolates was assessed using Vitek-2 system AST-YS08. **Results:** The age of patients with candidemia varied from 8 days to 85 years, with a higher occurrence observed among neonates and individuals aged 60-69 years. Higher rates of candidemia were observed in females than males (55.4% *versus* 44.6%). Among patients diagnosed with candidemia, *Candida albicans* was the most prevalent species, accounting for 52.7% of cases. Non-albicans *Candida* species represented 47.3% of cases; *C. parapsilosis* was the most predominant (18.9%), and *C. tropicalis* came in the second rank (16.2%). Fluconazole resistance among different *Candida* species was (20.3%), with no resistance recorded against amphotericin B, voriconazole, and micafungin. **Conclusions:** *Candida albicans* was the most commonly detected species, but there was an increased non-albicans *Candida* isolation rate. *Candida* isolates exhibited the highest resistance against fluconazole. Amphotericin B remained the most effective drug for treating *Candida* infections. The emergence of uncommon and multidrug-resistant *Candida* species highlights the need for surveillance and antifungal stewardship.

Introduction

Candidemia is a significant contributor to mortality and morbidity in healthcare settings, particularly in immunocompromised, critically ill individuals or patients suffering from complex medical disorders [1]. In recent years, a notable increase in the incidence of candidemia has been recorded, making it the fourth predominant cause of healthcare-associated bloodstream infections. Among critically ill patients and neonates, it ranks as the third predominant cause of bloodstream infections. Unfortunately, candidemia is linked to high fatality rates, ranging from 54% to 72% [2, 3].

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The epidemiology of candidemia varies across different geographical regions due to excessive use of broad-spectrum antibiotics, neutropenia, immunosuppressive medications, mechanical ventilation, indwelling medical device insertion, prolonged hospitalization, parenteral nutrition, and yeast colonization of multiple body sites. Infants under one year of age and elderly individuals over 65 years old tend to have higher rates of candidemia [3, 4].

Despite the predominance of *Candida albicans* (*C. albicans*) being the main detected species, a worldwide upsurge of non-albicans *Candida* (NAC) species has recently been recorded. Understanding the local patterns of *Candida* species distribution and their susceptibility profile to different antifungal medications is important since they fluctuate greatly between nations and are strongly affected by patients' underlying conditions [5]. Implementation of accurate and practical methods for identifying *Candida* species is essential for selecting appropriate antifungal treatments that can potentially save patients' lives [6]. Unfortunately, limited resources in laboratories, particularly in low-income nations like Egypt, often confine the diagnosis to either *C. albicans* or non-albicans, to minimize costs [7].

The rise in resistance amongst *Candida* species to different antifungal drugs has posed challenges in fungal infection treatment [8]. Owing to the vast heterogeneity in species distribution and susceptibility to antifungal drugs, it is essential to have local epidemiological data to guide effective treatment strategies for invasive candidiasis [9]. Therefore, this study aimed to investigate the distribution of *Candida* species and their susceptibility to antifungal drugs in critically ill patients with candidemia in a big tertiary care hospital in Egypt.

Materials and methods

Yeast-positive blood culture bottles BacT/ALERT 3D automated system (BioMérieux, Durham, NC, USA) from pediatric and adult intensive care units (ICU) of Kasr Alainy University Hospitals were collected from August 2022 to August 2023. Samples other than blood and blood cultures growing organisms other than yeast were excluded from the study.

The patients' age and sex information were obtained from the electronic medical records of the hospitals. The study was conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki and was approved by the Research Ethics Committee of Kasr Alainy, Faculty of Medicine, Cairo University, Egypt (N-187-2023). The patient's informed consent was not applicable because of the retrospective design of the study.

Identification of *Candida* up to species level

Yeast-positive blood culture bottles were subjected to Gram staining, followed by inoculation onto blood and Sabouraud dextrose agar plates (Oxoid, UK) and incubation overnight at 37 °C for 24-48 hours. A total of 74 *Candida* isolates were collected during the study period. The Vitek-2 yeast identification system (BioMérieux, France) was used to identify the isolates.

Antifungal susceptibility testing

The Vitek-2 system AST-YS08 (BioMérieux, France) was employed following the manufacturer's instructions to assess the minimum inhibitory concentrations (MICs) of various antifungal medications. The tested drugs included flucytosine, polyenes (amphotericin B), azoles (fluconazole, voriconazole), and echinocandins (caspofungin, micafungin). The MICs determined by the Vitek-2 were interpreted as resistant, intermediate, and susceptible using the species-specific clinical breakpoints of the Clinical and Laboratory Standards Institute (CLSI) [10].

Statistical analysis

The data were coded and entered into the statistical software package IBM SPSS version 28 (IBM Corp., Armonk, NY, USA). Descriptive statistics such as median, mean, standard deviation, minimum, and maximum were used to summarize quantitative data, while frequency (count) and relative frequency (%) were used for categorical data. Categorical data sets were compared using a Chi-square ($\chi 2$) test, and in cases where the expected frequency was less than 5, an exact test was used instead. Statistical significance was determined by *p-values* less than 0.05. Sample size estimation was performed by the Epi info statistical package. A total sample size of 62 isolates was needed to provide a two-sided 90% confidence interval for a single proportion using the large sample normal approximation and was extended 10% from the observed proportion for an expected proportion of 0.359. This was the minimum sample size required.

Results

Candida albicans was the most prevalent species among patients with candidemia (39/74,

52.7%), while NAC was isolated from 35/74 patients (47.3%) with *C. parapsilosis* was the most predominant NAC (18.9%) followed by *C. tropicalis* (16.2%). Each of *C lusitaniae* and *C. auris* was recovered from 3 cases (4.1%), the least predominant species were *C. krusei*, *C. glabrata*, and *C. guilliermondii* (1 patient, 1.4%) **(Figure 1)**.

Demographic data of patients

The patients' age ranged between 8 days to 85 years with a mean of 39.97 years. Candidemia was more common among neonates, and patients aged from 60 to 69 years (each 16.2%), followed by 70-79 years (14.9%), and patients aged between 30-39 years were the least affected group (5.4%). Higher rates of candidemia were observed in females than in males, 41 (55.4%) *versus* 33 (44.6%) respectively with no significant difference statistically.

There was no observed difference statistically between *C. albicans* and NAC species distribution among different age groups (*p-values* >0.05). It was observed that NAC species were recovered more commonly than *C. albicans* from neonates (20% *versus* 12.8%), young infants, and children aged more than 1 month to 9 years (17.1% *versus* 7.7%). *C. parapsilosis* was isolated mainly in the first 2 years of age (7/14, 50%). All *C. auris* isolates were recovered from old age ≥ 70 years (3/3, 100%) **(Table 1, Figure 2)**.

Antifungal susceptibility testing:

The results of *in-vitro* susceptibility testing to different antifungal drugs using Vitek-2 are illustrated in **Table 2**. *Candida* isolates exhibited the highest resistance against fluconazole (20.3%), and low resistance rates were observed against caspofungin and flucytosine (each 5.4%). No resistance was recorded against amphotericin B, voriconazole, and micafungin.

Regarding flucytosine; one isolate (2.6%) of *C. albicans* exhibited resistance to the drug, *versus* 3 isolates (8.6%) of NAC (one isolate of each *C. guilliermondii*, *C. krusei*, and *C. lusitaniae*). As regards fluconazole; 10 isolates (25.6%) of *C. albicans* showed resistance *versus* 5 isolates (14.3%) of NAC (4 isolates of C. *parapsilosis* and one isolate of *C. tropicalis*). Caspofungin resistance was recorded among 3 isolates (7.7%) of *C. albicans versus* 1 isolate (2.9%) of NAC (*C. guilliermondii*) **(Table 3, Figure 3)**.

Table 1. *C. albicans* and NAC distribution among different age groups

		Candida albicans		**non-albicans *Candida***		***p-value***
		Count	**%**	**Count**	**%**	
Age group	**Neonates (no.=12)**	5	12.8%	7	20.0%	0.403
	> 1 month-9 years (no.=9)	3	7.7%	6	17.1%	0.352
	10- 19 years (no.=3)	2	5.1%	1	2.9%	0.807
	20- 29 years (no.=7)	5	12.8%	2	5.7%	0.435
	30- 39 years (no.=4)	3	7.7%	1	2.9%	0.617
	40- 49 years (no.=5)	3	7.7%	2	5.7%	1
	50- 59 years (no.=5)	4	10.3%	1	2.9%	0.361
	60- 69 years (no.=12)	6	15.4%	6	17.1%	0.838
	70- 79 years (no.=11)	5	12.8%	6	17.1%	0.602
	> 80 years (no.=6)	3	7.7%	3	8.6%	1
Sex	**Male (no.=33)**	18	46.2%	15	42.9%	0.776
	Female (no.=41)	21	53.8%	20	57.1%	

Table 2. Antifungal susceptibility testing results by Vitek-2 of 74 *Candida* isolates

	Vitek-2								**Total (no.=74)**
	C. albicans (no=39)	Non-albicans *Candida* (no=35)							
		C. parapsilosis (no=14)	*C. tropicalis* (no=12)	*C. glabrata* (no=1)	*C. guilliermondii* (no=1)	*C. krusei* (no=1)	*C. lusitaniae* (no=3)	*C. auris* (no=3)	
Flucytosine S	38 (97.4%)	14 (100%)	12 (100%)	1 (100%)	0	0	2 (66.7%)	NA	67 (90.5%)
I	0	0	0	0	0	0	0	NA	0
R	1 (2.6%)	0	0	0	1 (100%)	1 (100%)	1 (33.3%)	NA	4 (5.4%)
Amphotericin B S	39 (100%)	14 (100%)	12 (100%)	1 (100%)	1 (100%)	1 (100%)	3 (100%)	NA	71 (95.9%)
I	0	0	0	0	0	0	0	NA	0
R	0	0	0	0	0	0	0	NA	0
Fluconazole S	29 (74.4%)	9 (64.3%)	10 (83.3%)	NA	NA	NA	NA	NA	48 (64.9%)
I	0	1 (7.1%)	1 (8.3%)	NA	NA	NA	NA	NA	2 (2.7%)
R	10 (25.6%)	4 (28.6%)	1 (8.3%)	NA	NA	NA	NA	NA	15 (20.3%)
Voriconazole S	39 (100%)	14 (100%)	12 (100%)	1 (100%)	1 (100%)	1 (100%)	3 (100%)	NA	71 (95.9%)
I	0	0	0	0	0	0	0	NA	0
R	0	0	0	0	0	0	0	NA	0
Caspofungin S	36 (92.3%)	14 (100%)	12 (100%)	1 (100%)	0	0	NA	NA	63 (85.1%)
I	0	0	0	0	0	1 (100%)	NA	NA	1 (1.4%)
R	3 (7.7%)	0	0	0	1 (100%)	0	NA	NA	4 (5.4%)
Micafungin S	39 (100%)	14 (100%)	12 (100%)	1 (100%)	NA	1 (100%)	NA	NA	67 (90.5%)
I	0	0	0	0	NA	0	NA	NA	0
R	0	0	0	0	NA	0	NA	NA	0

S= sensitive, I= intermediate, R= resistant, NA= not available
Vitek-2 system failed to detect the antifungal susceptibility testing of some species

Table 3. The resistance of *C. albicans* and NAC to different antifungal drugs

		Candida albicans		**Non-albicans *Candida***		***P-value***
		Count	**%**	**Count**	**%**	
Flucytosine	**R**	1	2.6%	3	8.6%	0.339
	No	38	97.4%	32	91.4%	
Amphotericin B	**R**	0	0.0%	0	0.0%	-----
	No	39	100.0%	35	100.0%	
Fluconazole	**R**	10	25.6%	5	14.3%	0.225
	No	29	74.4%	30	85.7%	
Voriconazole	**R**	0	0.0%	0	0.0%	-----
	No	39	100.0%	35	100.0%	
Caspofungin	**R**	3	7.7%	1	2.9%	0.617
	No	36	92.3%	34	97.1%	
Micafungin	**R**	0	0.0%	0	0.0%	-----
	No	39	100.0%	35	100.0%	

R= resistant, No= non-resistant

Figure 1. Percentage of *Candida* species recovered from ICU patients with candidemia.

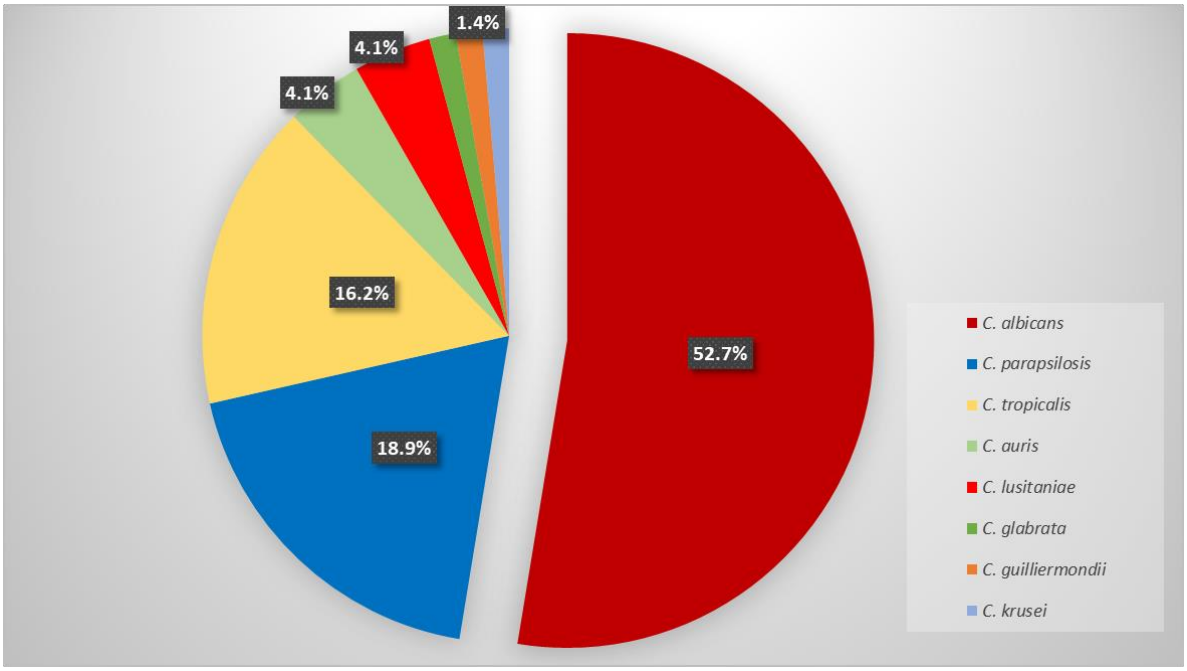


Figure 2. *Candida* species distribution in relation to the age of the patients**.**

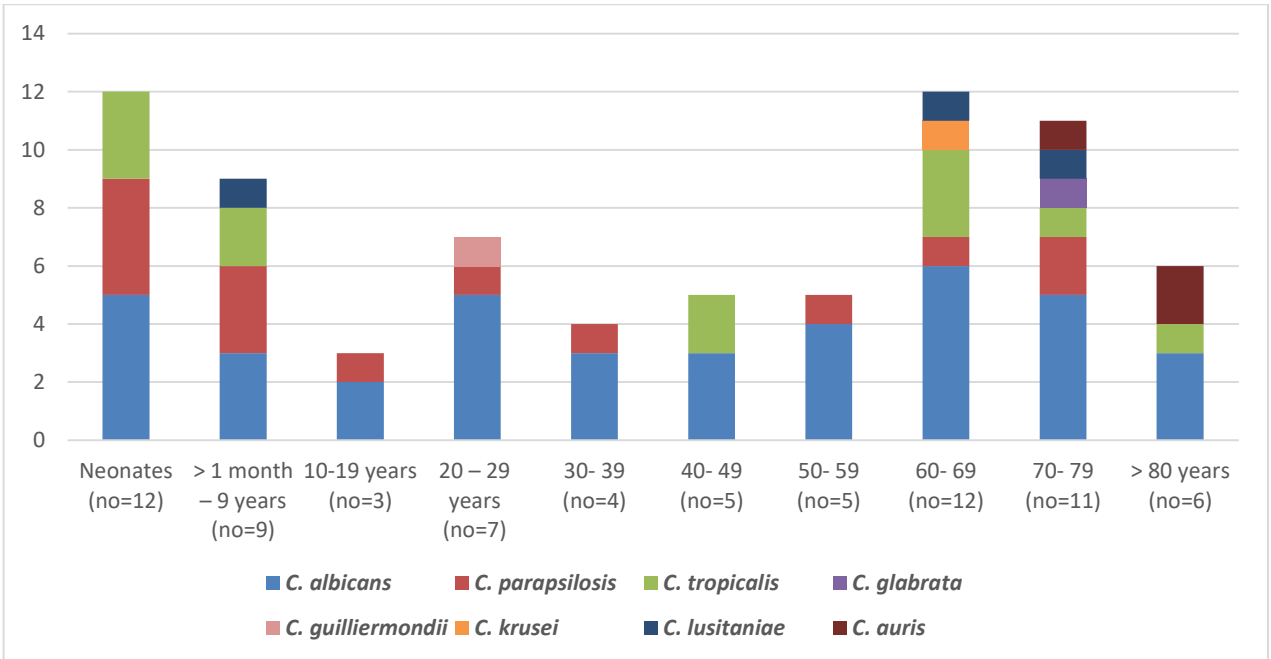
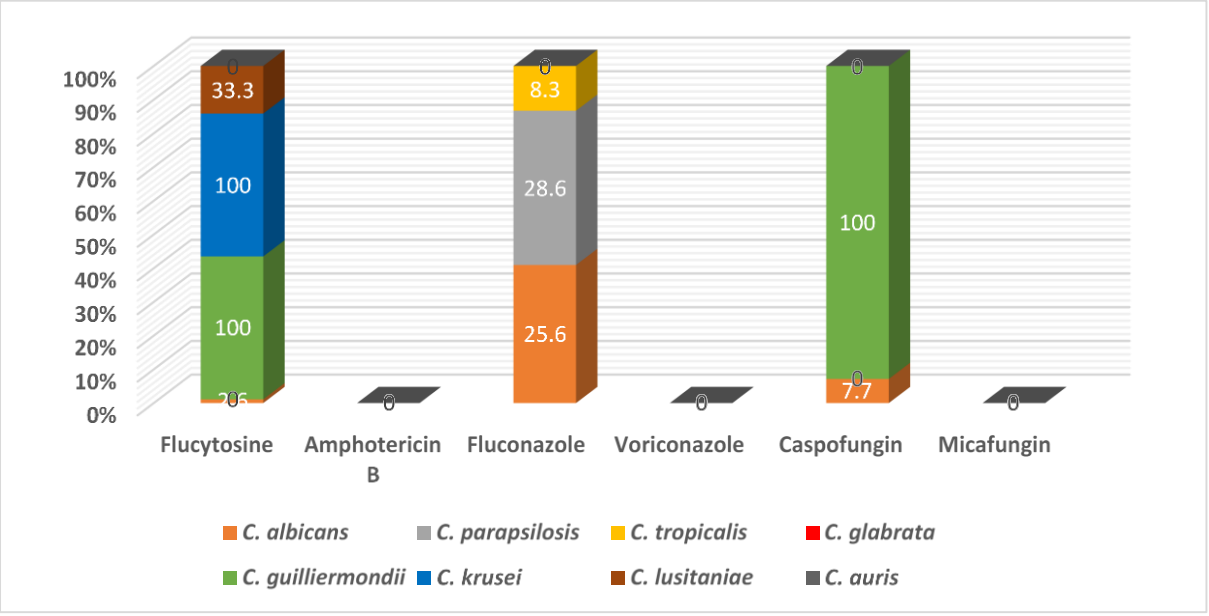


Figure 3. The percentage of resistance of *Candida* species to different antifungal drugs.



Discussion

Candidemia is a significant public health issue associated with high fatality rates, prolonged ICU stays, and a large financial burden **[**11]. We aimed to investigate the distribution of *Candida* species and their susceptibility to antifungal drugs in critically ill patients with candidemia.

In the current research, *C. albicans* was the most prevalent species (52.7%) from candidemia patients with an increased rate of NAC species isolation (47.3%). This was in agreement with previous Middle Eastern studies where *C. albicans* represented the most prevalent species with isolation rates of 74.3% in Tunisia, 56% in Lebanon, and Saudi Arabia [12, 13]. An observed rise in NAC species isolation rate was recorded in previous Egyptian and Middle Eastern studies, with percentages of 60%, 66.7%, 69.3% 74%, and 76% [14, 15].

Our study revealed that the most prevalent NAC species were *C. parapsilosis* (18.9%), then *C. tropicalis* (16.2%). Consistent with our results, other Middle Eastern studies found that *C. parapsilosis* predominated among NAC species in Egypt (25%), and Kuwait (22.6%) [14, 16]. **Ghazi et al.** found that *C. tropicalis* predominated in Tunisia (37.7%), and Saudi Arabia (15.5%). *C. glabrata* was found to be the most frequent species in Qatar, representing 25.5% of cases, and in Turkey, it was discovered in 13.3% of cases [15]. Uncommon species of *Candida* are increasingly identified in critically ill patients [17]. We reported 3 candidemia cases attributed to *C. auris* and *C lusitaniae* (4.1% each), and one caused by *C. guilliermondii* (1.4%). Several studies have isolated *C. lusitaniae and C. guilliermondii* from candidemia patients [18,19]. Consistent with our findings, research from Kuwait has shown that the multidrug-resistant species of *C. auris* emerged as a nosocomial pathogen associated with candidemia [16].

Neonates and young infants are more vulnerable to develop candidemia than adults, but interestingly, this age group tends to have a more favorable outcome [20]. In our study, candidemia was more common among neonates (16.2%) with the NAC species recovered more commonly than *C. albicans* (20% *versus* 12.8%) and from young infants and children aged more than 1 month to 9 years (17.1% *versus* 7.7%). Our results are supported by **Yılmaz-Ciftdoğan et al.** who found 73% of NAC candidemia among children compared to 26.9% of *C. albicans* candidemia [19]. Other studies demonstrated that pediatric patients exhibited the highest risk of developing candidemia compared to adult patients [21, 22]. In the present work, 50% of *C. parapsilosis* isolates were isolated mainly in the first 2 years of life. Research has consistently identified *C. parapsilosis* as the predominant NAC species frequently detected among infants and children. This prevalence has been linked to its ability to adhere to catheters, a

characteristic that facilitates its growth on plastic surfaces and its adaptation to parenteral nutrition environments [23].

In addition, a one-year research conducted in the pediatric ICU in Egypt revealed that *C. parapsilosis* was responsible for 25% of non-albicans candidemia, while *C. tropicalis* and *C. glabrata* coming in the second and third rank with 17% and 8% respectively [14]. On the other hand, studies from pediatric hospitals in Egypt and Saudi Arabia observed that *C. tropicalis* predominated among pediatric patients with candidemia [21, 24]. The species distribution may vary depending on the geographical region, sample size, length of hospital study, and certain patient risk factors including age and related co-morbidities like cancer, surgery, and central venous catheter implantation [25]. Furthermore, the empirical antifungal treatments utilized in the area may have an impact on species distribution. Research has shown that while the use of capofungin somewhat increases the risk of infection by *C. glabrata*, *C. parapsilosis* and *C. krusei*, fluconazole use increases the risk of *C. krusei* and *C. glabrata* infections [26].

The overall prevalence of antifungal resistance among *Candida* species is still relatively low. However, there is a growing trend of decreased susceptibility to azoles and echinocandins. Treatment of candidemia includes azoles, and echinocandins as primary therapeutic options [27, 28]. Our results revealed variable resistance patterns among isolated *Candida* species towards tested antifungal drugs. Regarding azole antifungals, the overall resistance to fluconazole was the most common (20.3%), while no resistance was recorded against voriconazole. Around 25.6 % of our *C. albicans* isolates exhibited resistance to fluconazole *versus* 14.3% of NAC isolates with no difference statistically (*p-value*=0.225). Several studies recorded an increase in the fluconazole resistance rate which can be explained by fluconazole is still the most frequently used antifungal medication [29, 30]. An Egyptian study conducted at the National Cancer Institute in 2023 reported an alarming rise in fluconazole and voriconazole resistance (58.3% and 16.7% respectively) among cancer patients with candidemia, with increasing resistance rates in NAC than *C. albicans* [31]. Among the NAC, *C. parapsilosis* showed the highest resistance to fluconazole (28.6%) in the present work. Of note, resistance to fluconazole in *C. parapsilosis* was considered rare, however, there has been a recent worldwide increase in fluconazole-resistant *C. parapsilosis* isolates [27].

Echinocandins, a group of antifungal drugs, have been in use for over two decades and recently advised as the initial treatment option for invasive candidiasis, particularly against azole-resistant *Candida* isolates [32]. The overall resistance to caspofungin remained very low for *Candida* isolates in the current work (5.4%), while no resistance was recorded among micafungin. Resistance to caspofungin was particularly notable against *C. albicans* isolates (7.7%) compared to NAC species (2.9)%. Despite being rare, multiple publications have shown that *C. albicans* exhibited resistance to caspofungin which was consistent with our findings [33, 34]. As reported in many studies, increased echinocandin resistance was often documented among *C. glabrata* isolates [35, 36]. However, we could not detect the actual percentage of echinocandin resistance among *C. glabrata* in our study, because one isolate only was identified as *C. glabrata*.

In our study, coresistance to fluconazole and caspofungin was detected in 2 isolates of *C. albicans*. Multidrug-resistant *Candida* species, which are primarily resistant to azoles, have grown due to the increased usage of echinocandins, such as caspofungin [33]. Another study recorded the presence of echinocandin resistance among eighteen isolates of fluconazole-resistant *C. glabrata* recovered from the bloodstream [37]. *C. parapsilosis* clinical isolates exhibited coresistance to azoles and echinocandins have also been documented [38].

Resistance to amphotericin B is still sporadic despite decades of use for this old antifungal [39]. In our study, no resistance to amphotericin B was detected among *Candida* isolates. This finding was consistent with previous Egyptian studies [40, 41]. It is worth noting that amphotericin B is not usually the primary treatment for invasive candidiasis in clinical settings, however, it might have an essential role in rescue treatment or when echinocandins and azoles are not effective [32].

There are limitations to consider in this study; including a small sample size of candidemia cases. Additionally, crucial data about underlying risk factors of patients, clinical history, and previous use of antifungals or antibiotics were lacking. These data could provide valuable insights into understanding the reasons behind candidemia

epidemiology. Uncommon *Candida* species like *C. auris* and *C. lusitaniae* could be misidentified by Vitek-2 systems, and it failed to detect the antifungal susceptibility testing of some species necessitating MALDI-TOF or molecular methods usage for identification and investigation of the resistance-associated molecular mechanisms.

Conclusion and recommendations

Candida albicans was identified as the predominant species in candidemia patients, but there was an increased occurrence of NAC species with the predominance of *C. parapsilosis*. *Candida* isolates exhibited the highest resistance against fluconazole. Amphotericin B continued to be the most effective drug for treating *Candida i*nfections. Uncommon species and multidrug-resistant *Candida* strains were emergent in our study emphasizing the importance of conducting multicenter research to investigate candidemia distribution and trends among critically ill patients. Surveillance and antifungal stewardship policies are crucial to minimize resistance.

Conflict of interest

All authors affirm no conflict of interest in the work.

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Authors' contributions

All authors have substantially contributed to the conception and design, acquisition of data, data analysis, and interpretation. All authors have agreed on the content of the manuscript.

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