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ORIGINAL RESEARCH

Clinical Features, Outcomes, and Antifungal Susceptibility Profiles of Invasive *Candida* Infections in a Tertiary Care Hospital in China

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Purpose: Given the increasing incidence of invasive *Candida* infection worldwide, particularly among immunocompromised and critically ill patients, we aimed to assess the distribution of *Candida* species as well as their clinical features and responses to common antifungal agents through a retrospective analysis of patient data in a Chinese traditional medicine hospital.

Patients and Methods: In this retrospective single-center study, we analyzed data from 301 patients with invasive *Candida* infection at our hospital between 2020 and 2022, We report the clinical characteristics, species distribution, and in-vitro susceptibility profiles of *Candida* isolates to eight antifungal agents. Logistic regression analysis was employed for multivariate assessments to analysis the correlation between clinical symptoms and prognosis. Kaplan–Meier survival analysis was used for survival analysis.

Results: *Candida albicans* was the most prevalent species (38.9%, 117/301), followed by *C. tropicalis* (28.2%, 85/301) and *C. glabrata* (22.9%, 69/301). Age, department of admission, underlying disease, and presence of risk factors differed significantly among patients with different *Candida* infections. Kaplan–Meier survival analysis showed that *C. krusei* infection was associated with a higher seven-day mortality than other *Candida* spp. infections. Multivariate logistic regression analyses showed that age, presence of sepsis, insertion of the central venous catheter, and administration of total parenteral nutrition were independent predictors of mortality. *C. tropicalis* was most resistant to azoles, with 36.26% of the strains being fluconazole-resistant, 35.16% being non-wild type to itraconazole, and 34.52% being non-wild type to voriconazole. Non-susceptibility to echinocandins was found in 11 *C. glabrata* strains (10.39%, 3.90%, and 1.30% of isolates for caspofungin, micafungin, and anidulafungin, respectively).

Conclusion: Our findings underscore the need for close monitoring of azole resistance in *C. tropicalis* and echinocandin resistance in *C. glabrata*, and highlight age, sepsis, CVC insertion, and parenteral nutrition as key predictors of mortality in invasive *Candida* infections.

Keywords: fungal disease, resistant, azoles, echinocandins

Introduction

Invasive *Candida* infection (ICI) is a common fungal disease, and its prevalence increases annually owing to growing susceptible populations.[1] The mortality rate of patients with ICI is approximately 20%, and patients in intensive care units (ICUs) have an even higher mortality rate.[2] *Candida* has a strong adhesive capacity and easily colonizes polystyrene, epithelium, and other surfaces to form biofilms, thereby becoming pathogenic.[3] Risk factors for pathogen colonization include central venous catheter (CVC) and administration of total parenteral nutrition. *Candida* not only causes mucosal diseases but also invades the internal organs or blood, causing systemic infections in patients with

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compromised immunity, such as those with diabetes and neutropenia, as well as in those who have received organ transplants.[4]

Although *C. albicans* is the most common pathogen associated with ICI, the pathogenicity rate for non-*albicans Candida* is increasing annually.[5] Moreover, the rate of drug resistance in *Candida* spp. is increasing owing to the widespread and long-term use of antifungals.[6] Notably, emerging drug resistance patterns, such as *C. tropicalis* resistance to azoles and *C. glabrata* resistance to echinocandins, have become critical issues in the management of ICI. The distribution of *Candida* spp. and susceptibility patterns vary according to country, region, center, and clinic, making comparisons among studies difficult.[7–9] Therefore, local epidemiologic information on ICI is critical for therapeutic management of the disease.

In traditional Chinese medicine hospitals, where the use of antifungal agents may differ from conventional medical settings, there is a significant gap in regional data regarding the epidemiology of ICI and antifungal resistance. This study aims to address this gap by providing detailed information on the species distribution and in vitro susceptibility of *Candida* isolates to eight antifungal agents in our hospital. In this study, we retrospectively analyzed data from patients with ICI at our hospital between 2020 and 2022. We aim to inform the selection of optimal clinical treatment options, enhance empirical antifungal treatment protocols, and support infection control measures, thereby improving overall clinical management of ICI.

Materials and Methods

Collection of Clinical Data

Clinical data from 301 patients with ICI were gathered retrospectively, encompassing demographics, admission departments, underlying conditions, potential risks, and outcomes. These patients were admitted to Longhua Hospital in Shanghai, China from January 2020 to December 2022. Longhua Hospital is a university hospital, affiliated to Shanghai University of Traditional Chinese Medicine, with 1000 beds, featuring 48 departments such as Internal Medicine, Surgery, Oncology, and Emergency Medicine. To ensure data completeness and relevance, the following exclusion criteria were applied: Patients with incomplete medical records that lacked essential information on demographics, underlying conditions, or treatment outcomes; patients who received antifungal treatment prior to sample collection, as this could influence the accuracy of antifungal susceptibility testing. In addition to the 301 inpatient samples, we included 55 *Candida* spp. strains isolated from outpatients. These outpatient samples were collected from various clinics within Longhua Hospital, shown in Table S1.

Ethical Approval and Data Confidentiality

Ethical approval for this study was obtained from the Medical Research Ethics Committee of Longhua Hospital. To ensure data confidentiality and patient anonymity, all patient records were de-identified prior to analysis, and only anonymized data were used in the study. Access to the data was restricted to the research team, and all data were stored securely in compliance with local data protection regulations.

Strains and Culture Conditions

Collectively, 301 *Candida* spp. strains were isolated from patients with ICI, and 55 strains were collected from outpatients at Long Hua Hospital. Species were identified through the use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. The strains were cultured on a yeast-peptone-dextrose medium at 30°C, as detailed previously.[10]

Antifungal Sensitivity Testing

Antifungal sensitivity was assessed using the broth microdilution technique, following the Clinical and Laboratory Standards Institute (CLSI) guidelines M27-A3.[11] Quality control was ensured by including reference strains (*Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC6258) in each batch of susceptibility testing. Susceptibility

breakpoints were assessed following the CLSI M27-M44S guidelines,[12] when applicable, while epidemiological cutoff values were determined based on CLSI M60,[13] CLSI M59,[14] and CLSI M27-S3.[15]

Statistical Analysis

A power analysis was conducted prior to the study to ensure adequate sample size for detecting significant associations. Based on previous studies and pilot data, we estimated that a sample size of 301 patients would provide 99% power to detect a significant association with a medium effect size (w = 0.3) at a significance level of $P < 0.05$. This calculation was performed using G*Power software (version 3.1).[16] Statistical analyses were performed using SPSS (version 24.0). The chi-squared test was employed to analyze proportions, and Fisher's exact test was used to analyze incomplete data. A statistical significance threshold was established at $P < 0.05$. Variables that were biologically plausible and $P < 0.1$ in the univariate analysis were incorporated into the multiple logistic regression model. Variables such as age, gender, and treatment regimens were included in the model to adjust for confounding effects. Kaplan–Meier survival analysis was used for survival analysis. Statistical significance was assessed using the Log rank test to compare survival differences between groups, with $P < 0.05$ indicating significant differences. During data analysis, we assessed the dataset for missing data points. No missing data existed in the covariates included in the analysis.

Results

Clinical Characteristics

Of the 301 strains isolated from patients with ICI, *C. albicans* (38.9%, 117/301) was the most common *Candida* species, followed by *C. tropicalis* (28.2%, 85/301) and *C. glabrata* (22.9%, 69/301).

Table 1 summarizes the characteristics and predisposing factors of the study participants. The mean age for the entire sample population was 77.86 years, and 160 (53.2%) of the patients were male. Patients with *C. parapsilosis* infection, of whom half (10/20) were aged 70 years or younger, were on average nine years younger than patients with other types of

Table 1 Clinical Characteristics of Patients With Infections Attributed to Different Candida Species

Characteristics	Total	*C. albicans*	*C. tropicalis*	*C. glabrata*	*C. parapsilosis*	*C. krusei*	*P* value
	(n=301)	(n=117)	(n=85)	(n=69)	(n=20)	(n=10)	
Gender, n (%)							0.125
Male	160 (53.2%)	55 (47.0%)	55 (64.7%)	35 (50.7%)	9 (45.0%)	6 (60.0%)	
Age, median±SD	77.86 ± 13.83	77.91 ± 13.38	79.51 ± 12.72	78.26 ± 14.11	68.65 ± 16.89	78.8 ± 15.37	0.036
<=70, n (%)	74 (24.4%)	26 (22.2%)	18 (21.2%)	17 (24.6%)	10 (50.0%)	3 (30%)	
71–80, n (%)	72 (23.8%)	28 (23.9%)	21 (24.7%)	15 (21.7%)	6 (30.0%)	2 (20%)	
81–90, n (%)	108 (35.6%)	51 (43.6%)	26 (30.6%)	26 (37.7%)	3 (15.0%)	2 (20%)	
>90, n (%)	47 (15.6%)	12 (10.3%)	20 (23.5%)	11 (15.9%)	1 (5.0%)	3 (30%)	
Department, n (%)							0.000
ICU	120 (39.9%)	65 (55.6%)	28 (32.9%)	21 (30.4%)	5 (25.0%)	1 (10%)	
Origin, n (%)							0.001
Urinary tract	112 (37.2%)	45 (38.5%)	29 (34.1%)	30 (43.5%)	6 (30.0%)	2 (20%)	
Upper respiratory	89 (29.4%)	30 (25.6%)	32 (37.6%)	20 (29%)	2 (10.0%)	5 (50%)	
Lower respiratory	50 (16.5%)	24 (20.5%)	12 (14.1%)	10 (14.5%)	1 (5.0%)	3 (30%)	
Other	50 (16.5%)	18 (15.4%)	12 (14.1%)	9 (13%)	11 (55.0%)	0 (0%)	
Underlying diseases, n (%)							
Lung disease	222 (73.8%)	90 (76.9%)	65 (76.5%)	51 (73.9%)	8 (40.0%)	8 (80%)	0.012
Hypertension	194 (64.5%)	75 (64.1%)	54 (63.5%)	46 (66.7%)	16 (80.0%)	3 (30%)	0.113
Cardiovascular	163 (54.2%)	65 (55.6%)	45 (52.9%)	38 (55.1%)	10 (50.0%)	5 (50%)	0.984
Cerebral infarction	147 (48.8%)	55 (47%)	45 (52.9%)	34 (49.3%)	9 (45.0%)	4 (40%)	0.884
Sepsis	107 (35.7%)	52 (44.4%)	23 (27.1%)	23 (33.3%)	8 (40.0%)	1 (10%)	0.042
Diabetes	104 (34.6%)	41 (35%)	32 (37.6%)	23 (33.3%)	6 (30.0%)	2 (20%)	0.820
Kidney disease	86 (28.6%)	30 (25.6%)	20 (23.5%)	23 (33.3%)	13 (65.0%)	0 (0%)	0.001

(*Continued*)

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Table 1 (Continued).

Characteristics	Total	*C. albicans*	*C. tropicalis*	*C. glabrata*	*C. parapsilosis*	*C. krusei*	*P* value
	(n=301)	(n=117)	(n=85)	(n=69)	(n=20)	(n=10)	
Urinary tract infection	84 (27.9%)	27 (23.1%)	23 (27.1%)	29 (42%)	3 (15.0%)	2 (20%)	0.037
Digestive tract disease	56 (18.6%)	22 (18.8%)	18 (21.2%)	11 (15.9%)	5 (25.0%)	0 (0%)	0.474
Tumor	56 (18.6%)	21 (17.9%)	17 (20%)	16 (23.2%)	2 (10.0%)	0 (0%)	0.359
Hepatobiliary disease	42 (14.0%)	17 (14.5%)	14 (16.5%)	10 (14.5%)	0 (0%)	1 (10%)	0.424
Immune system diseases	11 (3.7%)	5 (4.3%)	2 (2.4%)	3 (4.3%)	0 (0%)	1 (10%)	0.639
Multiple organ injury	9 (3%)	3 (2.6%)	2 (2.4%)	3 (4.3%)	1 (5.0%)	0 (0%)	0.875
Risk factors, n (%)							
Use of antimicrobial	262 (87.0%)	103 (88%)	78 (91.8%)	57 (82.6%)	15 (75.0%)	9 (90%)	0.228
Presence of CVC	174 (57.8%)	76 (65%)	41 (48.2%)	36 (52.2%)	15 (75.0%)	6 (60%)	0.061
Urine catheter	167 (55.5%)	75 (64.1%)	44 (51.8%)	35 (50.7%)	8 (40.0%)	5 (50%)	0.153
Previous surgery	166 (55.1%)	67 (57.3%)	45 (52.9%)	38 (55.1%)	12 (60.0%)	4 (40%)	0.827
Stomach tube	144 (47.8%)	66 (56.4%)	38 (44.7%)	27 (39.1%)	9 (45.0%)	4 (40%)	0.186
Total parenteral nutrition	82 (27.2%)	44 (37.6%)	18 (21.2%)	13 (18.8%)	4 (20.0%)	3 (30%)	0.027
Dialysis	18 (6.0%)	5 (4.3%)	3 (3.5%)	0 (0%)	10 (50.0%)	0 (0%)	0.000
Outcome, n (%)							0.008
Die within 7 days	13 (4.3%)	2 (1.7%)	3 (3.5%)	6 (8.7%)	0 (0%)	2 (20%)	
Die within 7–30 days	51 (16.9%)	26 (22.2%)	12 (14.1%)	9 (13%)	3 (15.0%)	1 (10%)	
Die within >30 days	19 (6.3%)	4 (3.4%)	4 (4.7%)	5 (7.2%)	4 (20.0%)	2 (20%)	
Survival, n (%)	218 (72.4%)	85 (72.6%)	66 (77.6%)	49 (71.0%)	13 (65.0%)	5 (50%)	

Notes: Handling of Missing Data: No missing data existed in the covariates included in the analysis. All variables were complete, ensuring the integrity of the dataset. Statistical Significance: All *P* presented in Table 1 are unadjusted for multiple comparisons.
Abbreviations: CVC, central venous catheter; ICU, intensive care unit; SD, standard deviation.

Candida infections. The incidence of ICI increased with age and was prevalent among patients aged 81–90 years (35.6%, 108/301). Moreover, 120 of the 301 patients (39.9%) were admitted to the ICU, where *C. albicans* was the most common species. Regarding the probable sources of ICI, the urinary tract (37.2%, 112/301) was the most frequently detected portal of entry, followed by the upper respiratory (including sputum and nasopharyngeal swabs) (29.4%, 89/301) and lower respiratory (including tracheal aspirates and bronchoalveolar lavage fluid) (16.5%, 50/301) tracts.

All patients had at least one underlying disease, the most common being lung infection (73.8%, 222/301), followed by hypertension (64.5%, 194/301) and cardiovascular disease (54.2%, 163/301). The most common risk factor for *Candida* infection was previous antimicrobial use (84.7%, 2255/301), followed by insertion of a CVC (56.5%, 170/301), use of a urinary catheter (54.2%, 163/301), and previous surgery (54.2%, 163/301). Significant differences in the percentages of lung disease, sepsis, kidney disease, and urinary tract infection, among underlying diseases, and total parenteral nutrition and dialysis, among risk factors, were observed among patients with different *Candida* infections. Patients infected with *C. albicans* were likely to suffer from sepsis and were commonly administered total parenteral nutrition. Patients infected with *C. glabrata* were likely to have urinary tract infections, patients infected with *C. parapsilosis* were likely to have kidney disease and require dialysis, and patients infected with *C. krusei* were likely to have lung disease.

Information on antifungal treatments administered to patients with ICI was collected and analyzed. The most commonly used antifungal agent was fluconazole (93.0%, 280/301). Other antifungal agents itraconazole and ketoconazole were used less frequently (2.3%, 7/301 and 3.0%, 9/301). Additionally, five patients were treated with a combination of two antifungal agents, including three treated with fluconazole and caspofungin.

Correlation Between Clinical Symptoms and Prognosis

The overall in-hospital mortality rate among the patients was 27.6% (83/301). Mortality was evaluated at different time intervals to provide a comprehensive understanding of the prognosis: 13 (4.3%) patients died within seven days after the diagnosis with *Candida* infection, 51 (16.9%) died within 7–30 days, and 19 (6.3%) died after 30 days. Patients with *C. krusei, C. parapsilosis*, and *C. glabrata* infections had an overall mortality rate of 50% (5/10), 35.0% (7/20), and

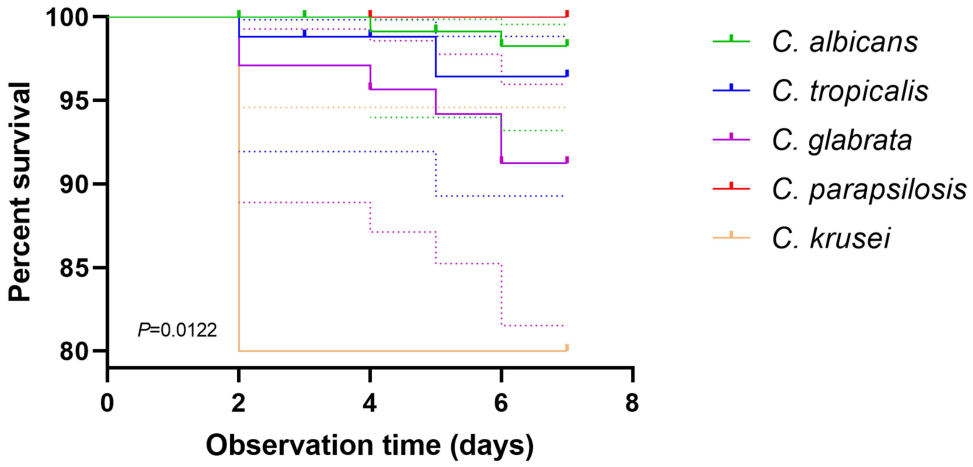

Figure 1 Analysis of seven-day patient survival trends for infections caused by different *Candida* spp. Kaplan–Meier survival curve was used to estimate the survival function from lifetime data. The sample size was 301 participants. Statistical significance was assessed using the Log rank test to compare survival differences between groups, with $P < 0.05$ indicating significant differences.

29.0% (20/69), respectively, whereas those with *C. albicans* and *C. tropicalis* infections had mortality rates of 27.4% (32/117) and 22.4% (19/85), respectively. Kaplan–Meier survival analysis showed that *C. krusei* infection led to a higher seven day-mortality rate than infection caused by other *Candida* spp. (P = 0.0122, Figure 1).

Table 2 shows the results of the univariate and multivariate logistic regression analyses performed to identify risk factors for mortality. For the primary endpoint analysis of mortality, we focused on the overall mortality rate during the entire follow-up period, which provides a comprehensive assessment of the long-term impact of invasive *Candida* infections. The statistical analysis showed no significant differences between the sexes. Among the three age groups, patients older than 85 years exhibited the highest mortality rate (33.7%, 35/104). Patients admitted to the ICU had a higher mortality rate (38.3%, 46/120). Among patients treated with fluconazole, the mortality rate was 28.9% (81/280), while those treated with a combination of antifungal agents was 40.0% (2/5). The univariate logistic regression analyses revealed that lung and cardiovascular disease and sepsis, among the underlying diseases, and use of antimicrobial, presence of CVC, urine catheter, or stomach tube, and use of total parenteral nutrition, among the risk factors, were

Table 2 Univariate and Multivariate Logistic Regression Analysis of Risk Factors for Mortality

Characteristics	Died	Survived	Univariate Analysis		Multivariate Analysis	
	(n=83)	(n=218)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Gender, n (%)						
Male	45 (28.1%)	115 (71.9%)	1.06 (0.64 ~ 1.76)	0.820	1.21 (0.64 ~ 2.29)	0.550
Age, median±SD	81.54 ± 10.977	76.45 ± 14.550				
<=70, n (%)	10 (13.5%)	64 (86.5%)	1.00 (Reference)		1.00 (Reference)	
71–85, n (%)	38 (30.9%)	85 (69.1%)	2.86 (1.33 ~ 6.17)	0.007	2.73 (1.14 ~ 6.53)	0.024
>85, n (%)	35 (33.7%)	69 (66.3%)	3.25 (1.49 ~ 7.09)	0.003	3.69 (1.46 ~ 9.32)	0.006
Department, n (%)						
ICU	46 (38.3%)	74 (61.7%)	2.42 (1.44 ~ 4.05)	< 0.001	0.65 (0.30 ~ 1.39)	0.265
Underlying diseases, n (%)						
Lung disease	68 (30.6%)	154 (69.4%)	1.88 (1.01 ~ 3.54)	0.049	0.61 (0.26 ~ 1.43)	0.258
Hypertension	57 (29.4%)	137 (70.6%)	1.30 (0.76 ~ 2.22)	0.346		
Cardiovascular	54 (33.1%)	109 (66.9%)	1.86 (1.10 ~ 3.14)	0.020	1.63 (0.86 ~ 3.08)	0.135
Cerebral infarction	38 (25.9%)	109 (74.1%)	0.84 (0.51 ~ 1.40)	0.513		
Sepsis	48 (44.9%)	59 (55.1%)	3.70 (2.18 ~ 6.27)	< 0.001	2.25 (1.11 ~ 4.58)	0.025

(*Continued*)

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Table 2 (Continued).

Characteristics	Died	Survived	Univariate Analysis		Multivariate Analysis	
	(n=83)	(n=218)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Diabetes	33 (31.7%)	71 (68.3%)	1.37 (0.81 ~ 2.31)	0.242		
Kidney disease	29 (33.7%)	57 (66.3%)	1.52 (0.88 ~ 2.61)	0.133		
Urinary tract infection	26 (31.0%)	58 (69.0%)	1.26 (0.72 ~ 2.19)	0.415		
Digestive tract disease	20 (35.7%)	36 (64.3%)	1.60 (0.87 ~ 2.97)	0.133		
Tumor	20 (35.7%)	36 (64.3%)	1.60 (0.87 ~ 2.97)	0.133		
Hepatobiliary disease	8 (19.0%)	34 (81.0%)	0.58 (0.26 ~ 1.30)	0.187		
Immune system diseases	1 (9.1%)	10 (90.9%)	0.25 (0.03 ~ 2.01)	0.194		
Multiple organ injury	5 (55.6%)	4 (44.4%)	3.43 (0.90 ~ 13.10)	0.071	2.99 (0.60 ~ 14.87)	0.180
Risk factors, n (%)						
Use of antimicrobial	78 (29.8%)	184 (70.2%)	2.88 (1.09 ~ 7.65)	0.033	0.91 (0.27 ~ 3.06)	0.878
Presence of CVC	72 (41.4%)	102 (58.6%)	7.44 (3.74 ~ 14.81)	< 0.001	6.48 (2.72 ~ 15.47)	<0.001
Urine catheter	72 (41.4%)	102 (58.6%)	3.45 (1.95 ~ 6.10)	< 0.001	1.09 (0.42 ~ 2.86)	0.855
Previous surgery	46 (27.7%)	120 (72.3%)	1.02 (0.61 ~ 1.69)	0.953		
Stomach tube	59 (41.0%)	85 (59%)	3.85 (2.23 ~ 6.65)	< 0.001	1.11 (0.43 ~ 2.87)	0.828
Total parenteral nutrition	38 (46.3%)	44 (53.7%)	3.34 (1.94 ~ 5.75)	< 0.001	2.00 (1.04 ~ 3.85)	0.039
Dialysis	1 (5.6%)	17 (94.4%)	0.14 (0.02 ~ 1.10)	0.062	0.14 (0.02 ~ 1.24)	0.077
Antifungal Treatment (n, %)						
Fluconazole	81 (28.9%)	199 (71.1%)	1.00 (Reference)		1.00 (Reference)	
Itraconazole	0 (0.0%)	7 (100.0%)	0.00 (0.00 ~ Inf)	0.991	0.00 (0.00 ~ Inf)	0.992
Ketoconazole	0 (0.0%)	7 (100.0%)	0.00 (0.00 ~ Inf)	0.99	0.00 (0.00 ~ Inf)	0.988
Combination	2 (40.0%)	3 (60.0%)	1.64 (0.27 ~ 9.99)	0.593	3.02 (0.23 ~ 38.89)	0.397

correlated with mortality. Among the patients with underlying diseases, those with sepsis had the highest mortality rate (44.9%, 48/107). Among the patients with risk factors, those administered total parenteral nutrition had the highest overall mortality rate (46.3%, 38/82). The multivariate logistic regression analyses showed that age, sepsis, CVC insertion, and total parenteral nutrition were independent predictors of mortality.

Antifungal Susceptibility

The results of the in-vitro susceptibility testing of the *Candida* isolates are summarized in Table 3. A total of 356 isolates were analyzed, including 55 collected from outpatients. All strains were generally sensitive to amphotericin and 5-fluorocytosine.

Among the azoles, the minimum inhibitory concentration value required to inhibit 90% of the isolates (MIC90) was lower for voriconazole (0.5 mg/L) than for fluconazole (16 mg/L) or itraconazole (8 mg/L). Of the isolates studied, 15.95% were fluconazole-resistant, 19.71% were itraconazole-non-wild type (NWT), and 14.77% were voriconazole-NWT. *C. tropicalis* was the most resistant to azoles, with 36.26% of the strains being fluconazole-resistant, 35.16% being itraconazole-NWT, and 34.54% being voriconazole-NWT.

All echinocandins showed good activity against most *Candida* spp. Overall, caspofungin had higher MIC90 values (0.25 mg/L) than micafungin (0.125 mg/L) and anidulafungin (0.125 mg/L). Non-susceptibility to echinocandins was found in 11 *C. glabrata* isolates (10.39%, 3.90%, and 1.30% for caspofungin, micafungin, and anidulafungin, respectively).

Discussion

Despite the availability of diagnostic and treatment methods, the risk of *Candida* infections has recently increased due to the use of broad-spectrum antimicrobial and immunosuppressive agents, total parenteral nutrition, and mechanical ventilation. The prevalence of ICI has increased from 3.8 to 29.3% since the 1990s,[17] whereas the rate of infection by

Table 3 In-Vitro Susceptibility of 356 Candida Isolates to Eight Antifungal Agents

Species (N)	Antifungal agent	MIC (μg/mL)			R or non-wild type (%)
		Range	50%	90%	
C. albicans (n=140)					
	5FC: Flucytosine	<4	<4	<4	0.00
	AMB: Amphotericin B	≤0.5	≤0.5	≤0.5	0.00
	FLC: Fluconazole	≤0.5–64	≤0.5	2	7.91
	ITC: Itraconazole	0.0625–4	0.125	0.5	5.80
	VRC: Voriconazole	≤0.0625–16	≤0.0625	0.0625	8.20
	MCF: Micafungin	≤0.0625–0.125	≤0.0625	0.0625	0.00
	CAS: Caspofungin	≤0.0625–0.125	0.0625	0.125	0.00
	AND: Anidulafungin	≤0.0625–0.125	0.0625	0.0625	0.00
C. tropicalis (n=95)					
	5FC: Flucytosine	≤4	≤4	≤4	0.00
	AMB: Amphotericin B	≤0.5	≤0.5	≤0.5	0.00
	FLC: Fluconazole	≤0.5–64	1	≥64	36.26
	ITC: Itraconazole	0.0625–16	0.5	16	35.16
	VRC: Voriconazole	≤0.0625–16	0.125	4	34.52
	MCF: Micafungin	≤0.0625–0.125	0.0625	0.0625	0.00
	CAS: Caspofungin	≤0.0625–0.25	0.0625	0.125	0.00
	AND: Anidulafungin	≤0.0625–0.25	0.0625	0.125	0.00
C. glabrata (n=77)					
	5FC: Flucytosine	≤4–16	≤4	≤4	0.00
	AMB: Amphotericin B	≤0.5	≤0.5	≤0.5	0.00
	FLC: Fluconazole	≤0.5–64	2	8	1.30
	ITC: Itraconazole	0.0625–16	0.125	2	29.87
	VRC: Voriconazole	≤0.0625–2	0.125	0.25	7.35
	MCF: Micafungin	≤0.0625–1	0.0625	0.0625	3.90
	CAS: Caspofungin	0.0625–16	0.125	0.25	10.39
	AND: Anidulafungin	≤0.0625–1	0.125	0.125	1.30
C. parapsilosis (n=33)					
	5FC: Flucytosine	≤4	≤4	≤4	0.00
	AMB: Amphotericin B	≤0.5–1	≤0.5	≤0.5	0.00
	FLC: Fluconazole	≤0.5–2	0.5	1	0.00
	ITC: Itraconazole	0.0625–1	0.125	0.25	3.03
	VRC: Voriconazole	≤0.0625	≤0.0625	≤0.0625	0.00
	MCF: Micafungin	0.0625–0.25	0.125	0.125	0.00
	CAS: Caspofungin	0.0625–0.5	0.125	0.25	0.00
	AND: Anidulafungin	0.125–0.5	0.25	0.5	0.00
C. krusei (n=11)					
	5FC: Flucytosine	≤4–16	≤4	≤4	0.00
	AMB: Amphotericin B	≤0.5	≤0.5	≤0.5	0.00
	FLC: Fluconazole	8–32	16	16	100.00
	ITC: Itraconazole	0.5–4	1	4	45.45
	VRC: Voriconazole	0.25–0.5	0.25	0.5	0.00
	MCF: Micafungin	0.0625–0.125	0.125	0.125	0.00
	CAS: Caspofungin	0.0625–0.25	0.125	0.25	0.00
	AND: Anidulafungin	0.125–0.5	0.125	0.25	0.00

(*Continued*)

Table 3 (Continued).

Species (N)	Antifungal agent	MIC (μg/mL)			R or non-wild type (%)
		Range	50%	90%	
All isolates (n=356)					
	5FC: Flucytosine	≤4–16	≤4	≤4	0.00
	AMB: Amphotericin B	≤0.5–1	≤0.5	≤0.5	0.00
	FLC: Fluconazole	≤0.5–64	1	16	15.95
	ITC: Itraconazole	0.0625–16	0.125	8	19.71
	VRC: Voriconazole	≤0.0625–16	≤0.0625	0.5	14.77
	MCF: Micafungin	≤0.0625–1	≤0.0625	0.125	0.84
	CAS: Caspofungin	≤0.0625–16	0.125	0.25	2.25
	AND: Anidulafungin	≤0.0625–1	≤0.0625	0.125	0.28

Abbreviations: 5FC, flucytosine; AMB, amphotericin B; FLC, fluconazole; ITC, itraconazole; VRC, voriconazole; MCF, micafungin; CAS, caspofungin; AND, anidulafungin; MIC, minimum inhibitory concentration; R, resistant.

non-*albicans Candida* among all pathogens has been increasing annually.[18] This study revealed that *Candida* isolates comprised five invasive species, of which *C. albicans* was the most abundant, followed by *C. tropicalis* and *C. glabrata*, and then *C. parapsilosis* and *C. krusei*. This strain distribution is consistent with that observed in several previous studies,[1,19] but also differed from that of other studies.[20–22] While our findings are consistent with global trends, they provide critical local data that can inform regional treatment protocols and infection control strategies.

This study describes the demographic and clinical characteristics of patients with ICI, the distribution of *Candida* species in patient specimens, and patient outcomes at our hospital between 2020 and 2022, along with the in-vitro susceptibility profiles of these isolates to eight antifungal agents. The *Candida* strains were mainly isolated from the urine and respiratory tracts of ICI patients. The use of urinary and tracheal catheters for patients with poor urine flow and inability to cough sputum increases the risk of *Candida* colonization, making the urinary and respiratory systems common sites of infection. Xu et al[23] and Ai Er Ken et al[24] obtained specimens from the blood. Strains isolated from blood are associated with high drug resistance and mortality rates, as can be deduced from the increased detection rate of non-*albicans Candida* in bloodstream infections in recent years,[7,25] complicating the treatment of candidiasis.

Our results showed that the *Candida* spp. strains had varying distributions across wards. ICI occurred more frequently among patients hospitalized in general wards than in those from ICUs. Among the patients admitted to the ICU with severe underlying diseases, older patients tended to have a high likelihood of becoming infected and developing ICI.[10,26,27] This is due to their relatively low level of immunity, which often necessitates the use of endotracheal tubes, CVCs, and other invasive procedures that facilitate *Candida* colonization. Previous studies have shown that *Candida* can be easily isolated from patients with impaired immunity,[28–30] which is consistent with our results.

ICI etiology varied according to age, hospitalization status, or underlying conditions of the patients. Clinical data were compared between patients with ICI caused by different species of *Candida*. Patients with *C. parapsilosis* infection were young and were likely to experience kidney disease or to require dialysis. Infection with *C. albicans* occurred frequently in patients with sepsis and in those who required administration of total parenteral nutrition. The mortality rate was higher after *C. krusei* infection than after infections caused by other *Candida* spp., indicating that infection by this species is more difficult to treat than those by other species. Infection is not only related to the pathogenicity of *Candida* species but also to complications associated with the patient's underlying disease. In our study, patients with one or more underlying diseases had increased mortality rates. The multivariate logistic regression analysis showed that age, presence of sepsis, CVC use, and administration of total parenteral nutrition were associated with increased mortality. Other studies have also shown a correlation between high mortality, underlying diseases, and the presence of risk factors.[31,32] The use of catheters facilitates *Candida* colonization, which further complicates treatment. Moreover, underlying diseases and immune-related disorders suppress the immune system and increase the risk of infection.[33] While the

identified mortality predictors are consistent with existing literature, they reinforce the importance of these factors in local clinical practice and can guide the development of targeted interventions.

The interaction between age, sepsis, and antifungal resistance patterns is complex. Older patients often have comorbidities and weakened immune systems, which increase their susceptibility to infections and antifungal resistance. Sepsis, as a severe systemic inflammatory response, can further impair immune function and increase the likelihood of *Candida* colonization and subsequent infection. Additionally, prolonged hospital stays and the use of invasive devices in older patients with sepsis can lead to higher exposure to antifungal agents, potentially contributing to resistance. Future studies should explore these interactions in more detail to better understand the underlying mechanisms.

Our study examines the antifungal treatments employed in patients with ICI and their potential influence on patient mortality. Our analysis revealed no significant differences in mortality rates between patients treated with different antifungal agents. This finding may be attributed to the high prevalence of fluconazole use, which limits the statistical power to detect differences in mortality rates associated with other antifungal agents. Fluconazole remains a viable empirical treatment option for many patients, although its efficacy may be influenced by factors such as antifungal resistance and the severity of underlying conditions. Despite the lack of significant differences in mortality, our findings highlight the importance of considering alternative antifungal agents, particularly in patients with high-risk factors or those who do not respond to initial fluconazole therapy. The use of combination therapy, such as fluconazole and caspofungin, may be beneficial in certain cases, although further studies are needed to confirm its efficacy and safety.

The sensitivity of *Candida* species to antifungal agents was also analyzed; azoles and echinocandins are commonly used antifungal drugs for treating ICI. The results showed that although most strains were sensitive to azoles, resistance to itraconazole was the highest (19.71%), whereas the rates of strain resistance to fluconazole and voriconazole were 15.95% and 14.77%, respectively. *C. tropicalis* was the most resistant to azoles, and *C. glabrata* was non-susceptible to echinocandins. The drug resistance exhibited by these strains may be due to the long-term use of antifungal drugs.[34,35] All *Candida* strains were sensitive to both 5-flucytosine and amphotericin. Although 5-flucytosine and amphotericin are not first-line antifungals in the treatment of ICI in most clinical contexts, they may substitute azoles or echinocandins or be used in salvage therapy.[36,37] The resistance patterns observed in our study have significant implications for empirical therapy and antifungal stewardship. Empirical treatment protocols should consider these resistance patterns, especially in high-risk populations such as ICU patients and those with underlying sepsis. Antifungal stewardship programs should be implemented to monitor and optimize antifungal use, reducing the risk of resistance development.

To contextualize our findings within the broader scope of research on ICI, we compared our results on antifungal resistance rates with those from other studies conducted in China. In our study, *C. tropicalis* exhibited relatively high resistance rates to azole antifungal, which are similar to the national data reported by Xiao et al,[1] but higher than that reported by Li et al[38] in a Tertiary Care Hospitals in Western China, where the fluconazole resistance rate was 5.9%. For echinocandin antifungals, resistance was only observed in *C. glabrata*, consistent with the findings of Zhang et al[39] and Song et al.[40] However, the resistance rates varied across studies. The disparities in resistance rates could be connected to the regional use of antifungals, the types of hospitals, and the demographics of the patient populations. This highlights the importance of local epidemiology and drug resistance surveillance in guiding clinical management and treatment strategies.

The findings of this study carry significant implications for clinical practice. First, given the high azole resistance rate in *C. tropicalis* and the presence of echinocandin-non-susceptible *C. glabrata* strains, we propose revising local empirical antifungal treatment guidelines: for critically ill or high-risk patients (eg, those with long-term central venous catheters or receiving total parenteral nutrition), initial therapy should prioritize echinocandins over fluconazole to cover potential resistance risks; for non-critical patients, a step-down approach guided by susceptibility testing is recommended. Second, infection control strategies must be strengthened, including strict adherence to catheter insertion and maintenance protocols (eg, daily assessment of catheter necessity), implementation of active fungal colonization screening in high-risk wards (eg, ICUs), and establishment of real-time resistance surveillance networks to detect nosocomial transmission early. Furthermore, this study underscores the urgency of Antifungal Stewardship Programs (ASPs). For instance, azole resistance in *C. tropicalis* may correlate with prolonged exposure. ASP-driven strategies, such as restriction policies for broad-spectrum azoles, therapeutic drug monitoring, and duration optimization, could attenuate resistance development.

Finally, integrating rapid molecular diagnostics (eg, MALDI-TOF MS combined with resistance gene detection) could significantly shorten species identification and susceptibility reporting times. For example, *FKS* gene mutation testing in *C. glabrata* could guide targeted echinocandin use, avoiding treatment delays and unnecessary drug exposure. The comprehensive implementation of these measures may improve outcomes in invasive candidiasis and curb the spread of resistant strains.

Our research had certain constraints. First, the retrospective design inherently carries risks of incomplete documentation of clinical details and microbiological data, as well as potential recall bias during data collection. Second, the single-center nature of the investigation may limit the generalizability of our findings, as regional variations in antifungal resistance patterns and population-specific risk factors might not be adequately represented. Third, the lack of standardized protocols for patient management protocols during the study period, including antifungal treatment regimens and ICU care protocols, introduces potential variability in treatment outcomes that could not be fully accounted for in the analysis. Nevertheless, we are confident that our findings offer clinicians valuable insights prior to devising empirical treatment plans for patients with ICI and contribute to understanding the epidemiology and risk factors associated with ICI.

Conclusion

Our study provides insights into the epidemiology, clinical outcomes, and antifungal resistance patterns of ICI in a traditional Chinese medicine hospital setting, highlighting the importance of local data for guiding clinical practice. Our findings emphasize the need for tailored empirical antifungal therapy, particularly prioritizing echinocandins (eg, anidulafungin) for high-risk patients, such as those with prolonged central venous catheterization or total parenteral nutrition, while adopting de-escalation strategies for non-critical cases guided by rapid susceptibility testing. Based on these results, the implementation of antifungal stewardship programs (ASPs) is essential to mitigate resistance trends. This is particularly achieved through restriction policies for broad-spectrum azoles, therapeutic drug monitoring, and optimized treatment durations. Additionally, enhanced infection control measures are also imperative to curb nosocomial transmission. These measures include standardized catheter maintenance protocols, proactive fungal colonization surveillance in high-risk units, and real-time resistance monitoring networks. The public health significance of the increasing antifungal resistance is extremely important. The rising prevalence of non-*albicans Candida* species and their resistance to first-line antifungals pose a substantial threat to global health, particularly in immunocompromised populations. Our findings call for heightened vigilance and coordinated efforts to monitor resistance patterns, promote rational antifungal use, and integrate advanced diagnostic tools (eg, MALDI-TOF MS and *FKS* mutation assays) into routine clinical workflows. These measures are vital for improving patient outcomes and preserving the efficacy of existing antifungal agents. This study has limitations, including its single-center, retrospective design, which may limit the generalizability of the findings. Future multicenter, prospective studies are needed to validate our observations and explore the impact of integrated traditional Chinese medicine-Western therapies on antifungal resistance.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article. The datasets are available from the corresponding author on reasonable request.

Ethics Approval

This retrospective study was approved by the Medical Research Ethics Committee of Longhua Hospital; individual data were collected anonymously and the requirement to obtain informed written consent was waived. This study was conducted in accordance with the Declaration of Helsinki.

Consent to Publish

Patient consent to publish was waived due to the retrospective nature of the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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