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Original Article

Epidemiology, clinical features, antifungal resistance, and prognosis of fungemia in pediatric patients

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Abstract

Introduction: The aim of this study was to investigate the epidemiology, clinical characteristics, antifungal susceptibility, and prognosis of fungemia among pediatric patients.

Methodology: A retrospective cohort analysis was conducted on 195 fungemia cases at Guangxi Zhuang Autonomous Region Maternal and Child Health Hospital over a 7-year period (2016–2023). Comprehensive clinical data were extracted from the electronic medical record system.

Results: Microbiological analysis of 195 fungemia cases revealed 22 distinct fungal species. *Candida parapsilosis* was the predominant pathogen (28.2%, 55/195), followed by *Candida albicans* (26.7%, 52) and *Candida tropicalis* (10.8%, 21). The cohort demonstrated distinctive epidemiological features: median patient age of 30 days, neonatal predominance (40.5%), and male preponderance (60%). Alarmingly high antifungal resistance profiles were observed, particularly in *C. albicans* (66% fluconazole and 62% voriconazole resistance) and *C. dubliniensis* (82% itraconazole resistance). Non-albicans infections correlated with elevated intensive care unit (ICU) admission rates and neutropenia incidence, while *C. albicans* cases showed stronger associations with prematurity and low birth weight. The clinical course was marked by prolonged hospitalization (median 37 days), with 56.4% requiring intensive care and 20% developing persistent candidemia. 81.5% achieved clinical resolution, though 15.4% required non-medical transfers and 3.0% succumbed to refractory infections despite maximal therapy.

Conclusions: Neonates represented the highest-risk population for pediatric fungemia, with a median hospitalization duration of 37 days. Over half of the affected children (56.4%) required ICU admission. The high rate of antifungal resistance and poor prognosis underscore the urgent need for enhanced surveillance protocols and optimized antifungal stewardship in pediatric settings.

Key words: fungemia; prognosis; candidemia; pediatric.

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Introduction

Fungal infections, particularly bloodstream infections (fungemia), pose a significant health risk to pediatric populations, especially among vulnerable groups such as neonates and immunocompromised children [1–3]. The primary pathogens responsible for fungemia are *Candida*, *Aspergillus*, *Cryptococcus*, *Fusarium*, and members of Zygomycetes, with *Candida* being the most common [4–6]. Epidemiological studies have demonstrated a progressive escalation in fungemia risk associated with the expanding utilization of broad-spectrum antimicrobial agents, immunosuppressive therapies, and invasive clinical procedures [7,8]. Surveillance data from US healthcare facilities indicate an incidence rate of 1.03–1.19 cases per 10,000 hospital admissions; and this burden appears substantially higher in resource-limited settings [9].

The incidence and impact of these infections have garnered increased attention in recent years, highlighting the pressing need for comprehensive epidemiological data and effective treatment strategies. Currently, the clinical characteristics and prognosis of pediatric fungemia are not well understood, and variations exist in the distribution of infecting fungal species and drug resistance across different regions [10,11]. In this study, data from 195 cases of pediatric fungemia treated at a hospital between July 2016 and October 2023 were retrospectively analyzed. The aim was to describe the local epidemiology, clinical features, species distribution, antifungal drug susceptibility, and prognosis of pediatric fungemia.

Methodology

Study population

This was a retrospective analysis of hospitalized children with fungal bloodstream infections admitted to the Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region from July 2016 to October 2023. A total of 3,212 positive fungal culture samples from the microbiology laboratory (Figure 1) were screened initially, of which 203 were from blood cultures. Two duplicate samples from the same patient were excluded. Next, patients were excluded based on the following criteria: age ≥ 18 years (2 cases), and incomplete or missing case data (4 cases). Ultimately, a total of 195 patients with fungemia were recruited, including 52 cases of *Candida albicans* fungemia and 143 cases of non-albicans fungemia. The patients' clinical information and laboratory test data were also recorded.

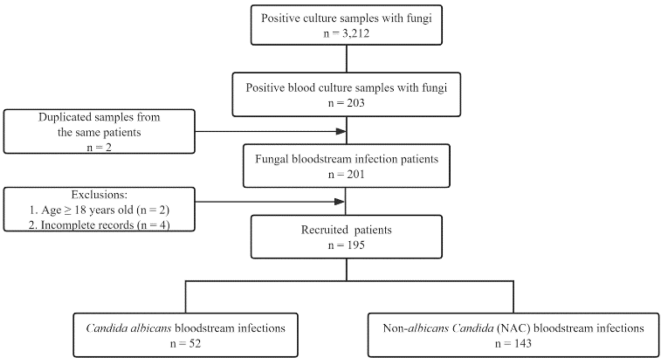
Ethical considerations

The study was approved by the Medical Ethics Committee of the Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region (No. 2022–005). The Ethics Committee decided to waive the need for informed consent from patients due to the retrospective nature of the study. In order to ensure patient privacy, all patient identifiers—such as names, hospital ID numbers, and admission dates—were removed from the dataset, and the data was anonymized using a unique coding system accessible only to the principal investigator.

Microbiological testing

The blood samples were separated under sterile conditions and cultured in the BD BACTEC FX (Becton Dickinson Diagnostic Instrument Systems, Franklin Lakes, NJ, USA) blood culture system for 5–7 days. Positive culture bottles were Gram stained and then inoculated onto three types of agar plates: Columbia blood agar (Guangzhou Dijie Microbial Technology Co Ltd, Guangzhou, China), chocolate agar (Guangzhou Dijie Microbial Technology Co Ltd, Guangzhou, China), and Sabouraud agar (Zhengzhou Antu Bioengineering Co, Ltd., Zhengzhou, China). The cultures were incubated at 37 °C for 24 hours, and then the fungal species are identified using the Yeast-Like Fungal Identification Plate (Zhuhai Di'er Biomedical Engineering Co Ltd, Zhuhai, China) or the fully automated microbial mass spectrometry detection system Autof ms600 (Autobio Laboratory Instruments Co Ltd, Zhengzhou, China). Subsequently, antifungal susceptibility testing was performed using the Di'er Biological Reagent Strips (Zhuhai Di'er Biomedical Engineering Co Ltd, Zhuhai, China) to evaluate in vitro resistance to fluconazole, voriconazole, 5-fluorocytosine, itraconazole, and amphotericin B. *Candida albicans* ATCC90029 was employed as a quality control strain. The *Candida* isolates were categorized as susceptible (S), intermediate (I), and resistant (R) according to the minimum inhibitory concentrations (MIC) and based on the clinical breakpoints (CBPs) for antifungal drugs [12].

Figure 1. Flow diagram of patient recruitment.



Definitions

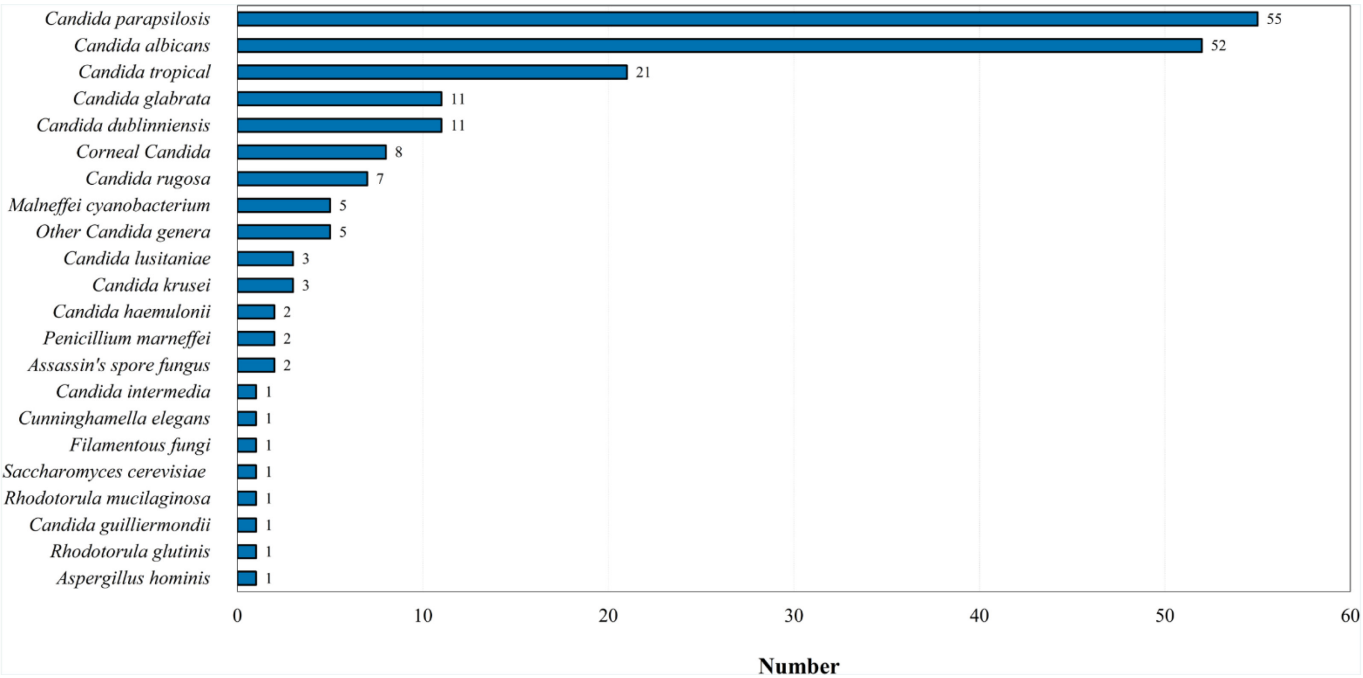
Fungemia diagnosis was established in accordance with the 2016 Infectious Diseases Society of America (IDSA) guidelines [13], mandating concurrent satisfaction of microbiological and clinical criteria. The microbiological criterion required ≥ 1 positive blood culture for fungi (excluding *Candida* spp. skin commensals from single culture). The clinical requirement was the presence of ≥ 2 systemic inflammatory response syndrome (SIRS) criteria which include core temperature > 38.3 °C or < 36 °C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min, and white blood cell count > 12 × 10⁹/L or < 4 × 10⁹/L.

Persistent candidemia (PC) was defined as the isolation of the same *Candida* species from positive blood culture for ≥ 5 days after the initiation of antifungal therapy [14].

Statistical methods

IBM SPSS statistics 26.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analyses. Quantitative data satisfying normal distribution and equal variance were expressed as mean ± standard deviation (x ± s); and the independent samples t-test was used to compare groups. Median (interquartile range, IQR) was used for data with non-normal distribution; and the non-parametric rank-sum test was used to compare groups. Qualitative data were expressed as frequency

Figure 2. Distribution of fungal species in the 195 cases of pediatric bloodstream infections.



(percentages), and the Chi-square test was used for comparison between groups. Differences were considered statistically significant at $p < 0.05$.

Results

Distribution and epidemiology of the fungal species

A total of 195 pediatric patients with fungemia were investigated from July 2016 to October 2023. Among the 22 fungal species identified (Figure 2), the five most frequently observed were *Candida parapsilosis* (55 cases, 28.2%), *Candida albicans* (52 cases, 26.7%), *Candida tropicalis* (21 cases, 10.8%), *Candida dubliniensis* (11 cases, 5.6%), and *Candida glabrata* (11 cases, 5.6%).

Figure 3 illustrates the number of pediatric patients diagnosed with fungemia over the years. The highest number of detections occurred in 2019. After that, there was a downward trend, with the fewest cases recorded in 2022 (Figure 3). Additionally, the distribution of fungal species varied across the years. Infections in 2016 and 2022 were primarily caused by *C. albicans*, whereas *C. parapsilosis* was the dominant species in the other years (Figure 4). Analysis of the differences in distribution of the common fungal species across

Figure 3. Number of pediatric fungemia cases detected across various years.

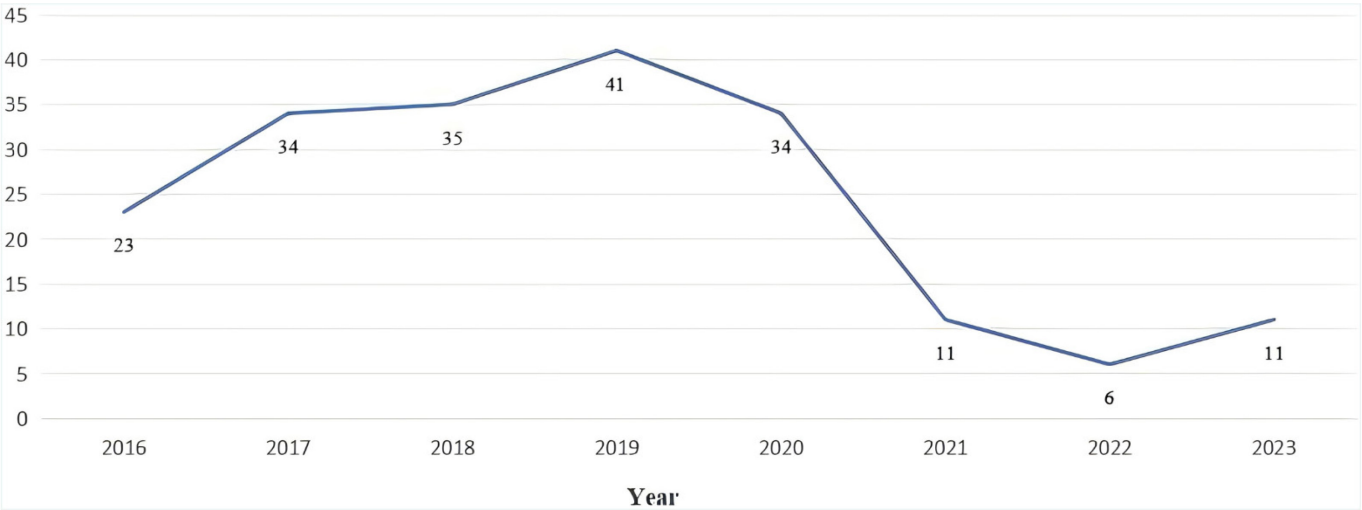
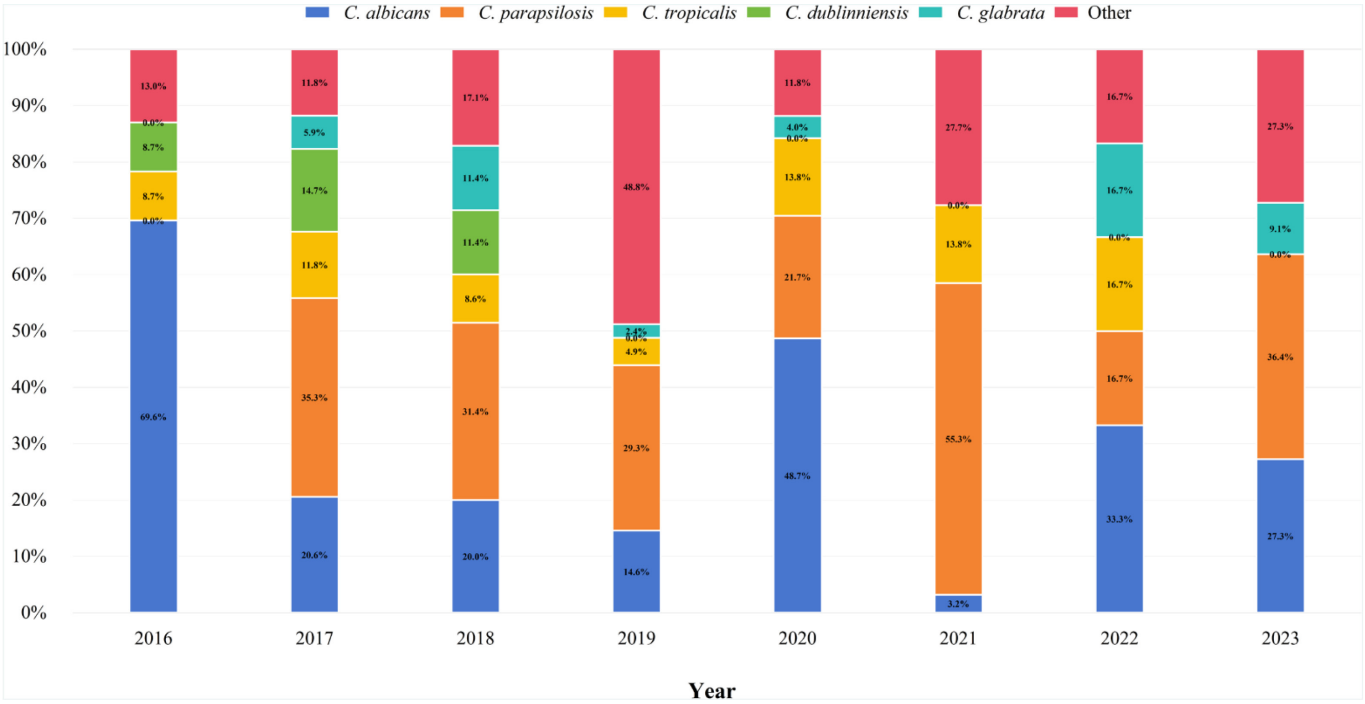


Figure 4. Trends in the fungemia species distribution from 2016 to 2023.



genders revealed that *C. albicans* infections exhibited a significant gender disparity, with male patients being significantly more predominant than females. No statistically significant differences in gender distribution were observed among patients with the other fungal species (Supplementary Table 1).

Patient characteristics and laboratory testing

Table 1 provides an overview of the key characteristics of the infected children. The median age of the children was 30 days (IQR, 20–120 days), and 60% (117 out of 195) were male. Of all patients with fungemia, 40.5% (79 out of 195) were neonates, 53.8% (105 out of 195) were preterm infants, and 34.9% (68 out of 195) were classified as low-birth-weight infants.

Table 1. Clinical characteristics of patients with *Candida albicans* and non-*albicans Candida* candidemia.

Characteristics	Total (n = 195)	*C. albicans* (n = 52)	NAC (n = 143)	*p* value
Male gender, n (%)	117 (60.0%)	37 (71.2%)	80 (55.9%)	0.055
Age (days), median (IQR)	30 (20,120)	30 (19,60)	30 (20,150)	0.255
Neonates (< 28 days), n (%)	79 (40.5%)	24 (46.2%)	55 (38.5%)	0.333
Preterm infants, n (%)	105 (53.8%)	37 (71.2%)	68 (47.6%)	**0.003***
Low birthweight infants, n (%)	68 (34.9%)	26 (50%)	42 (29.4%)	**0.008***
ICU admission, n (%)	110 (56.4%)	45 (86.5%)	65 (45.5%)	**< 0.001***
Length of hospitalization (days), median (IQR)	37 (24,62)	45 (30,57)	35 (22,63)	0.284
Basic diseases				
Respiratory	98 (50.3%)	33 (63.5%)	65 (45.5%)	**0.026 ***
Gastrointestinal	89 (45.6%)	16 (30.8%)	73 (51.0%)	**0.012 ***
Nervous	42 (21.5%)	14 (26.9%)	28 (19.6%)	0.270
Hematological	4 (2.1%)	1 (1.9%)	3 (2.1%)	0.934
Risk factors				
Surgery, n (%)	96 (33.3%)	20 (38.5%)	76 (53.1%)	0.819
Blood transfusion, n (%)	141 (72.3%)	38 (73.1%)	103 (72.0%)	0.885
Prior antibiotics exposure, n (%)	168 (86.2%)	46 (88.5%)	122 (85.3%)	0.574
Presence of CVC, n (%)	80 (41.0%)	24 (46.2%)	56 (39.2%)	0.380
Presence of urethral catheter, n (%)	88 (45.2%)	12 (23.1%)	76 (53.1%)	**< 0.001 ***
Presence of abdominal drainage tube, n (%)	51 (26.2%)	10 (19.2%)	41 (28.7%)	0.185
Temperature > 38 °C	51 (26.2%)	15 (28.9%)	36 (25.2%)	0.606
Temperature < 36 °C	9 (4.6%)	2 (3.8%)	7 (4.9%)	0.758
WBC < 4.0×10^9 /L, n (%)	24 (12.3%)	7 (13.5%)	17 (11.9%)	0.767
NC < 1.5×10^9 /L, n (%)	18 (9.2%)	1 (1.9%)	17 (11.9%)	**0.034 ***

***$p < 0.05$** represents statistically significant differences. *C. albicans: Candida albicans*; NAC: non-*albicans Candida*; ICU: intensive care unit; CVC: central venous catheter; WBC: white blood count; NC: neutrophil count.

Table 2. Comparison of laboratory test results between *Candida albicans* and non-*albicans Candida* candidemia.

Variables	Total (n = 195)	*C. albicans* (n = 52)	NAC (n = 143)	*p* value
HBG (g/L), x ± s	107.9 ± 22.8	108.6 ± 24.9	107.6 ± 22.1	0.163
WBC ($\times 10^9$), median (IQR)	8.3 (5.8, 12.1)	7.5 (5.8, 10.3)	8.4 (5.8, 13.1)	0.106
NC ($\times 10^9$), median (IQR)	4.6 (2.7, 7.5)	4.7 (2.9, 7.6)	4.6 (2.7, 7.5)	0.821
LC ($\times 10^9$), median (IQR)	2.1 (1.0, 4.3)	1.8 (1.2, 3.3)	2.4 (1.4, 4.4)	0.051
NLR, median (IQR)	2.1 (1.0, 4.0)	2.6 (1.2, 4.0)	1.8 (0.9, 4.0)	0.152
PLT ($\times 10^9$), median (IQR)	182 (104, 288)	135 (76.3, 280.8)	195 (108, 294)	0.051
ALB (g/L), median (IQR)	31.8 (27.9, 36.7)	30.2 (27.8, 32.6)	32.1 (28.1, 38.5)	**0.030***
TB (g/L), median (IQR)	36.7 (14.5, 99.0)	38.4 (20.1, 99.0)	36.3 (11.8, 101.7)	0.480
ALT (g/L), median (IQR)	17.0 (8.0, 40.0)	14.5 (6.0, 51.0)	20.0 (10.0, 37.0)	0.204
AST (g/L), median (IQR)	39.0 (23.0, 76.0)	31.5 (23.0, 78.3)	39.0 (24.0, 83.0)	0.284

***$p < 0.05$** represents statistically significant differences. *C. albicans*: *Candida albicans*; NAC: non-*albicans Candida*; HBG: hemoglobin; WBC: white blood count; NC: neutrophil count; LC: Lymphocyte count; NLR: neutrophil to lymphocyte ratio; PLT: platelets; ALB: albumin; TB: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Patients with non-albicans fungemia required intensive care at a higher rate and had a greater incidence of neutropenia compared to those with *C. albicans* fungemia. Additionally, there was a significantly higher proportion of patients with underlying gastrointestinal diseases and indwelling catheters in the non-albicans group. In contrast, the group with *C. albicans* fungemia had a significantly higher proportion of preterm infants, low-birth-weight infants, and infants with respiratory system diseases. All these differences were statistically significant ($p < 0.05$) (Table 1). When comparing laboratory test indicators between the *C. albicans* group and the non-albicans group in children, only serum albumin was slightly higher in the non-albicans group. Other indicators did not show statistically significant differences ($p > 0.05$; Table 2).

In vitro susceptibilities

C. albicans exhibited high resistance rates to fluconazole and voriconazole, reaching approximately 66% and 62%, respectively. *C. tropicalis* and *C.*

Table 3. Comparison of antifungal susceptibilities of different *Candida* spp. in vitro.

Species/Antifungal agent	Number[b]	WT/S (%)	SDD, n (%)	I, n (%)	NWT/R, n (%)
C. albicans **(n = 52)**					
Fluconazole	50	NA	NA	NA	33 (66%)
Amphotericin Ba	50	50 (100%)	NA	NA	0
5-fluorocytosine	50	NA	NA	NA	NA
Itraconazole	50	NA	NA	NA	NA
Voriconazole	50	13 (26%)	NA	6 (12%)	31 (62%)
C. parapsilosis **(n = 55)**					
Fluconazole	55	NA	NA	NA	0
Amphotericin Ba	55	40 (72.73%)	NA	NA	15 (27.27%)
5-fluorocytosine	55	NA	NA	NA	NA
Itraconazolea	55	55 (100%)	NA	NA	0
Voriconazole	55	51 (92.73%)	NA	4 (7.27%)	0
C. tropicalis **(n = 21)**					
Fluconazole	21	NA	NA	NA	10 (47.62%)
Amphotericin B[a]	21	21 (100%)	NA	NA	0
5-fluorocytosine	21	NA	NA	NA	NA
Itraconazole[a]	21	11 (52.38%)	NA	NA	10 (47.62%)
Voriconazole	21	6 (28.57%)	NA	5 (23.81%)	10 (47.62%)
C. Glabrata **(n = 11)**					
Fluconazolea	10	6 (60%)	NA	NA	4 (40%)
Amphotericin Ba	10	10 (100%)	NA	NA	0
5-fluorocytosine	10	NA	NA	NA	NA
Itraconazolea	10	6 (60%)	NA	NA	4 (40%)
Voriconazolea	10	6 (60%)	NA	NA	4 (40%)
C. dubliniensis **(n = 11)**					
Fluconazole	11	NA	NA	NA	NA
Amphotericin B	11	NA	NA	NA	NA
5-fluorocytosine	11	NA	NA	NA	NA
Itraconazolea	11	2 (18%)	NA	NA	9 (82%)
Voriconazole	11	NA	NA	NA	NA

WT/S: wild type/susceptible; I: intermediate; SDD: susceptible dose dependent; NWT/R: non-wild type/resistant; NA: not available; *C. albicans*: *Candida albicans*; *C. parapsilosis*: *Candida parapsilosis*; *C. tropicalis*: *Candida tropicalis*; *C. glabrata*: *Candida glabrata*; *C. dubliniensis*: *Candida dubliniensis*. [a] Epidemiological cutoff values (ECV) were used to interpret the results when no Clinical and Laboratory Standards Institute (CLSI) breakpoints were available. [b] Number of isolated species tested for antifungal susceptibility.

glabrata typically exhibited elevated resistance rates to fluconazole, itraconazole, and voriconazole; ranging from approximately 40% to 48%. *C. dubliniensis* had an exceptionally high resistance rate to itraconazole, at 82%. *C. parapsilosis* was relatively sensitive to azole antifungal drugs, and exhibited a resistance rate of 27% to amphotericin B (Table 3).

Prognosis

Among the 195 pediatric patients with fungemia, the median hospital stay was 37 days (IQR, 24–62 days). Of these, 110 patients (56.4%) required admission to the intensive care unit (ICU) for monitoring. Out of the 195 patients with fungemia, 39 (20%) had persistent candidemia. After active treatment, 159 patients (81.5%) showed improvement and were discharged; 30 patients (15.4%), were transferred to another hospital at their families' request due to unsatisfactory outcomes. Additionally, 6 (3.0%) patients died due to ineffective treatment.

Outcome predictors in candidemia

Logistic regression models were subsequently employed to predict patient outcomes (Table 4). Univariate analysis identified ICU admission, presence of a central venous catheter (CVC), and prolonged hospitalization as risk factors for candidemia-associated poor prognosis; whereas higher albumin (ALB) levels served as a protective factor against adverse outcomes. In the multivariate analysis, the presence of a CVC (OR, 2.347; 95% CI, 1.031–5.348; p = 0.042), hypoalbuminemia (low ALB levels; OR, 0.934; 95% CI, 0.880–0.992; p = 0.025), and prolonged hospitalization (OR, 1.020; 95% CI, 1.003–1.040; p = 0.025) emerged as independent risk factors for candidemia-related adverse prognosis.

Discussion

The distribution of fungal species in fungemia varies by region. A multicenter retrospective study in the United States found that *C. albicans* accounted for 39% of cases; and *C. glabrata* and *C. parapsilosis* followed at 28% and 15%, respectively [15]. Similarly, two other studies conducted in Zhejiang, China, and Greece reported that *C. albicans* was the most common species in candidemia, accounting for 46.5% and 41.0% of cases, respectively [16,17]. Additionally, a study in Anhui, China, revealed that *C. tropicalis* had a higher incidence at 33.0%; compared to *C. albicans*, which accounted for 27.8%; making it the leading cause of

Table 4. Logistic regression analysis of risk factors associated with poor outcomes in patients with candidemia.

Variables	Good prognosis group (n = 159)	Poor prognosis group (n = 36)	Univariate analysis *p* value	Multivariate analysis odds ratio (95% CI)	Multivariate analysis *p* value
Categorized variables [n, (%)]					
Gender (male)	96 (60.4)	21 (58.3)	0.821		
Neonate	67 (42.1)	12 (33.3)	0.333		
ICU admission	17 (10.7)	13 (36.1)	***< 0.001**	2.564 (0.988–6.623)	0.053
Respiratory system	76 (47.8)	22 (61.1)	0.152		
Gastrointestinal system	69 (43.4)	20 (55.6)	0.188		
Nervous system	31 (19.5)	11 (30.6)	0.149		
Hematological system	1 (0.6)	3 (8.3)	0.243		
Surgery	55 (34.6)	10 (27.8)	0.435		
Blood transfusion	115 (72.3)	26 (72.2)	0.990		
Prior antifungals exposure	64 (40.3)	14 (38.9)	0.880		
Prior antibiotic exposure	134 (84.3)	34 (94.4)	0.129		
Presence of CVC	59 (37.1)	21 (58.3)	***0.021**	2.347 (1.031–5.348)	***0.042**
Presence of urethral catheter	69 (43.4)	19 (52.8)	0.309		
Presence of abdominal drainage tube	42 (26.4)	9 (25.0)	0.862		
Temperature > 38 ℃	37 (23.3)	14 (38.9)	0.057		
Temperature < 36 ℃	7 (4.4)	2 (5.6)	0.766		
WBC < 4.0×10^9/L	18 (11.3)	6 (16.7)	0.381		
Neu < 1.5×10^9/L	14 (8.8)	4 (11.1)	0.667		
Quantitative variable [M (IQR)]					
WBC ($\times 10^9$)	8.1 (5.9)	8.3 (8.0)	0.127		
Neu ($\times 10^9$)	4.6 (4.4)	4.4 (7.4)	0.267		
Lym ($\times 10^9$)	2.0 (3.1)	2.4 (2.5)	0.481		
PLT ($\times 10^9$)	184 (191)	127 (173)	0.171		
ALB (g/L)	32 (10)	30 (7)	***0.019**	0.934 (0.880–0.992)	***0.025**
TBil (g/L)	39 (91)	30 (61)	0.747		
AST (g/L)	39 (45)	46 (132)	0.183		
ALT (g/L)	17 (29)	25 (76)	0.289		
Length of hospitalization (days)	42 (36)	26 (33)	***0.008**	1.020 (1.003–1.040)	***0.025**
Age (days)	30 (71)	45 (344)	0.244		

***$p < 0.05$** represents statistically significant differences. CVC: central venous catheter; WBC: white blood cell; Neu: neutrophil; Lym: lymphocyte; PLT: platelet; ALB: serum albumin; TBil: total bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

candidemia [18]. In this study the three most common pathogens detected in fungemia were *C. parapsilosis* (28.2%), *C. albicans* (26.7%), and *C. tropicalis* (10.8%); which differs from previous reports. The escalating incidence of *C. parapsilosis*-associated fungemia can be attributed to three interrelated factors. First, the pathogen's intrinsic traits—including robust adhesion capabilities, a propensity to colonize glucose-rich medical solutions, and a documented potential to drive nosocomial outbreaks—enable its persistence in healthcare settings [19]. Second, regional environmental conditions in Guangxi, notably sustained high humidity and elevated temperatures, create an ecological niche that amplifies fungal colonization on medical devices and hospital surfaces. These conditions specifically potentiate *C. parapsilosis* biofilm development which is a critical virulence determinant [20]. Third, molecular adaptations distinguish *C. parapsilosis* from other *Candida* species: its superior biofilm-forming capacity generates structured microbial communities that resist environmental stressors and exhibit intrinsic tolerance to antifungal agents [21].

The analysis of pediatric fungemia cases over the years revealed an increasing trend from 2016 to 2019. This was followed by a gradual decline in cases in the subsequent years. However, an upward trend reemerged after 2022. The points of change align with the timing of policy shifts in China's coronavirus disease 2019 (COVID-19) control measures. The domestic COVID-19 outbreak began at the end of 2019, and the country remained under COVID-19 control measures until the relaxation of these restrictions at the end of 2022. During this control period, enhanced protective measures, increased awareness, travel restrictions, and bans on gatherings effectively reduced the risk of infection by pathogens.

In this study of 195 pediatric patients with fungemia, the median age was 30 days (IQR, 20–120 days), and 40.5% were neonates. The proportions of preterm infants and low birth weight infants were 53.8% and 34.9%, respectively. Preterm and low birth weight infants are the primary population affected by pediatric fungemia due to several factors: 1) Their immature immune systems make them more vulnerable to fungal infections; 2) They often require invasive medical interventions that raise the risk of infection; 3) Prolonged use of broad-spectrum antibiotics can disrupt normal flora, allowing opportunistic pathogens, including fungi, to thrive; 4) These infants may also suffer from other chronic conditions, such as hematological disorders, which heighten their risk of developing fungemia.

A comparison of clinical data between pediatric patients with *C. albicans* fungemia and those with non-albicans fungemia, found a significantly higher proportion of preterm and low birth weight infants in the *C. albicans* group. This suggests that these two groups are more susceptible to *C. albicans* infection. Conversely, the proportion of patients requiring intensive care and the incidence of neutropenia were significantly higher in the non-albicans fungemia group, indicating that patients infected with non-albicans fungi have more severe conditions.

Antifungal resistance in pediatric candidemia has emerged as a critical global health concern. A multicenter study from South Africa revealed species-specific fluconazole resistance rates: 17% in *C. parapsilosis*, with no resistance observed in *C. tropicalis* or *C. albicans*. All isolates remained susceptible to amphotericin B and echinocandins [22]. Neonatal candidemia data from Brazil demonstrated 42.8% fluconazole resistance in *C. albicans*, including 21.4% dose-dependent susceptibility; while all isolates retained full susceptibility to amphotericin B [23]. A surveillance study conducted in Italy over five years highlighted escalating azole resistance, with 69.12% of non-albicans *Candida* species exhibiting resistance, notably higher in pediatric populations compared to adults [24]. Pediatric studies conducted in Turkey reported divergent resistance patterns: *C. albicans* and *C. parapsilosis* showed fluconazole resistance rates of 9.5% and 46.6%, respectively; and amphotericin B resistance of 1.1% and 7.6%, respectively [25]. Strikingly, the susceptibility testing in this study uncovered alarmingly elevated resistance profiles: *C. albicans* exhibited fluconazole and voriconazole resistance rates of 66% and 62%, respectively; while *C. tropicalis* and *C. glabrata* demonstrated resistance ranging from 40% to 48% across fluconazole, itraconazole, and voriconazole. These resistance rates substantially exceed most global benchmarks reported to date, underscoring the urgent need for region-specific antifungal stewardship and resistance surveillance programs.

Among the 195 pediatric patients with fungemia, the median hospital stay was 37 days, with a range of 24 to 62 days. Additionally, 56.4% of these children required admission to the ICU for monitoring. After active treatment, 81.5% of the patients showed improvement and were discharged. However, 18.5% of the patients had a poor prognosis, which included 15.4% who did not respond well to treatment and were transferred for further care, and 3.0% who died due to

ineffective treatment. The mortality rate reported in this study is lower than that in previous literature, which ranges from 21% to 70% [1,26–29]. The observed discrepancy in mortality rates can be attributed to three primary factors. First, the study populations differ significantly. This research focused exclusively on pediatric patients, whereas prior investigations predominantly included high-risk cohorts such as cancer patients, solid organ transplant recipients, elderly individuals, and patients with chronic comorbidities. Second, substantial advancements in diagnostic and therapeutic technologies have been implemented, including the adoption of rapid molecular diagnostics such as metagenomics next-generation sequencing (mNGS), and targeted next-generation sequencing (tNGS) for early pathogen identification; combined with advanced life-support modalities like extracorporeal membrane oxygenation (ECMO) for managing refractory septic shock. Third, integrating specialized pediatric intensive care protocols characterized by early multidisciplinary interventions and aggressive source control has led to significant reductions in mortality in the management of pediatric candidemia.

This study had several limitations. It was a single-center study with a relatively small sample size. The retrospective analysis carried inherent limitations, including potential selection bias and missing patient data. In addition, potential co-infecting pathogens were not systematically detected.

Conclusions

This study delineates critical epidemiological and clinical patterns in pediatric fungemia, revealing *C. parapsilosis* as the predominant etiological agent (detection rate: 28.2%). The cohort exhibited distinctive clinical signatures, including a median age of 30 days (IQR 20–120), prolonged hospitalization (median duration 37 days, IQR 24–62), and substantial intensive care utilization (56.4% ICU admission rate); collectively underscoring the heightened vulnerability of neonates to disseminated fungal infections. Notably, 18.5% of cases manifested poor outcomes, necessitating proactive implementation of risk mitigation strategies targeting modifiable prognostic determinants.

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Conflict of interest

No conflict of interest is declared.

References

1. Oeser C, Vergnano S, Naidoo R, Anthony M, Chang J, Chow P, Clarke P, Embleton N, Kennea N, Pattnayak S, Reichert B, Scorrer T, Tiron I, Watts T, Sharland M, Heath PT, Neonatal Infection Surveillance Network (neonIN) (2014) Neonatal invasive fungal infection in England 2004–2010. Clin Microbiol Infect 20: 936–941. doi: 10.1111/1469-0691.12578.
2. Kekana D, Naicker SD, Shuping L, Velaphi S, Nakwa FL, Wadula J, Govender NP, for GERMS-SA1 (2023) *Candida auris* clinical isolates associated with outbreak in neonatal unit of tertiary academic hospital, South Africa. Emerg Infect Dis 29: 2044–2053. doi: 10.3201/eid2910.230181.
3. Comes-Escoda A, Villaronga-Flaque M, Velasco-Arnaiz E, Esteban E, Pertierra-Cortada A, Noguera-Julian A (2024) Renal fungus balls in neonates and very young infants treated with local amphotericin B deoxycholate: two case reports and review of the literature. Enferm Infecc Microbiol Clin (Engl Ed) 42: 38–41. doi: 10.1016/j.eimc.2023.02.003.
4. Oz Y, Yilmaz M, Bulduk T, Basayigit M, Gunduz E, Metintas S (2024) Comparison of fungemia caused by *Candida* and non-*Candida* rare yeasts: a retrospective study from a tertiary care hospital. Med Mycol 62: myae037. doi: 10.1093/mmy/myae037.
5. Alves J, Palma P, Azevedo D, Rello J (2018) Candidemia in the patient with malignancy. Hosp Pract (1995) 46: 246–252. doi: 10.1080/21548331.2018.1508290.
6. Pasha AK, Lee JZ, Low SW, Desai H, Lee KS, Al Mohajer M (2016) Fungal endocarditis: update on diagnosis and management. Am J Med 129: 1037–1043. doi: 10.1016/j.amjmed.2016.05.012.
7. Miceli MH, Diaz JA, Lee SA (2011) Emerging opportunistic yeast infections. Lancet Infect Dis 11: 142–151. doi: 10.1016/S1473-3099(10)70218-8.
8. Kanj SS, Haddad SF, Meis JF, Verweij PE, Voss A, Rautemaa-Richardson R, Levy-Hara G, Chowdhary A, Ghafur A, Bruggemann R, Bal AM, Schouten J (2023) The battle against fungi: lessons in antifungal stewardship from COVID-19 times. Int J Antimicrob Agents 62: 106846. doi: 10.1016/j.ijantimicag.2023.106846.
9. Bretagne S, Sitbon K, Desnos-Ollivier M, Garcia-Hermoso D, Letscher-Bru V, Cassaing S, Millon L, Morio F, Gangneux JP,

Hasseine L, Favennec L, Cateau E, Bailly E, Moniot M, Bonhomme J, Desbois-Nogard N, Chouaki T, Paugam A, Bouteille B, Pihet M, Dalle F, Eloy O, Sasso M, Demar M, Mariani-Kurkdjian P, Robert V, Lortholary O, Dromer F, French Mycoses Study Group (2022) Active surveillance program to increase awareness on invasive fungal diseases: the French RESSIF Network (2012 to 2018). mBio 13: e0092022. doi: 10.1128/mbio.00920-22.

10. Caggiano G, Lovero G, De Giglio O, Barbuti G, Montagna O, Laforgia N, Montagna MT (2017) Candidemia in the neonatal intensive care unit: a retrospective, observational survey and analysis of literature data. Biomed Res Int 2017: 7901763. doi: 10.1155/2017/7901763.
11. Falagas ME, Roussos N, Vardakas KZ (2010) Relative frequency of albicans and the various non-albicans *Candida* spp among candidemia isolates from inpatients in various parts of the world: a systematic review. Int J Infect Dis 14: e954–966. doi: 10.1016/j.ijid.2010.04.006.
12. Clinical and Laboratory Standards Institute (2022) Performance standards for antifungal susceptibility testing of yeasts, M27. 4nd ed. Clinical and Laboratory Standards Institute.
13. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD (2016) Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 62: e1–50. doi: 10.1093/cid/civ933.
14. Li Y, Gu C, Yang Y, Ding Y, Ye C, Tang M, Liu J, Zeng Z (2023) Epidemiology, antifungal susceptibility, risk factors, and mortality of persistent candidemia in adult patients in China: a 6-year multicenter retrospective study. BMC Infect Dis 23: 369. doi: 10.1186/s12879-023-08241-9.
15. Toda M, Williams SR, Berkow EL, Farley MM, Harrison LH, Bonner L, Marceaux KM, Hollick R, Zhang AY, Schaffner W, Lockhart SR, Jackson BR, Vallabhaneni S (2019) Population-based active surveillance for culture-confirmed candidemia - four sites, United States, 2012-2016. MMWR Surveill Summ 68: 1–15. doi: 10.15585/mmwr.ss6808a1.
16. Liu F, Zhong L, Zhou F, Zheng C, Zhang K, Cai J, Zhou H, Tang K, Dong Z, Cui W, Zhang G (2021) Clinical features, strain distribution, antifungal resistance and prognosis of patients with non-albicans candidemia: a retrospective observational study. Infect Drug Resist 14: 3233–3246. doi: 10.2147/IDR.S323583.
17. Siopi M, Tarpatzi A, Kalogeropoulou E, Damianidou S, Vasilakopoulou A, Vourli S, Pournaras S, Meletiadis J (2020) Epidemiological trends of fungemia in Greece with a focus on candidemia during the recent financial crisis: a 10-year survey in a tertiary care academic hospital and review of literature. Antimicrob Agents Chemother 64: e01516–1519. doi: 10.1128/AAC.01516-19.
18. Ye N, Liu Z, Tang W, Li X, Chu W, Zhou Q (2022) Systematic characterization of epidemiology, antifungal susceptibility, risk factors and outcomes of candidemia: a six-year Chinese study. Infect Drug Resist 15: 4887–4898. doi: 10.2147/IDR.S378629.
19. Blyth CC, Chen SC, Slavin MA, Serena C, Nguyen Q, Marriott D, Ellis D, Meyer W, Sorrell TC, Australian Candidemia Study (2009) Not just little adults: candidemia epidemiology, molecular characterization, and antifungal susceptibility in neonatal and pediatric patients. Pediatrics 123: 1360–1368. doi: 10.1542/peds.2008-2055.
20. Welsh RM, Bentz ML, Shams A, Houston H, Lyons A, Rose LJ, Litvintseva AP (2017) Survival, persistence, and isolation of the emerging multidrug-resistant pathogenic yeast *Candida auris* on a plastic health care surface. J Clin Microbiol 55: 2996–3005. doi: 10.1128/JCM.00921-17.
21. Silva S, Negri M, Henriques M, Oliveira R, Williams DW, Azeredo J (2011) Adherence and biofilm formation of non-*Candida albicans Candida* species. Trends Microbiol 19: 241–247. doi: 10.1016/j.tim.2011.02.003.
22. Gebremicael MN, Nuttall JJC, Tootla HD, Khumalo A, Tooke L, Salie S, Muloiwa R, Rhoda N, Basera W, Eley BS (2023) *Candida* bloodstream infection among children hospitalized in three public-sector hospitals in the Metro West region of Cape Town, South Africa. BMC Infect Dis 23: 67. doi: 10.1186/s12879-023-08027-z.
23. da Silva CM, de Carvalho AMR, Macêdo DPC, Jucá MB, Amorim RJM, Neves RP (2023) Candidemia in Brazilian neonatal intensive care units: risk factors, epidemiology, and antifungal resistance. Braz J Microbiol 54: 817–825. doi: 10.1007/s42770-023-00943-1.
24. Meneghello S, Bernabè G, Di Pietra G, Di Sopra S, Del Vecchio C, Cattelan AM, Castagliuolo I, Brun P (2024) Prevalence, species distribution and resistance of candidemia in pediatric and adult patients in a northeast Italy university hospital. J Fungi (Basel) 10: 707. doi: 10.3390/jof10100707.
25. Guner Ozenen G, Sahbudak Bal Z, Avcu G, Ozkaya Yazici P, Karakoyun M, Metin DY, Hilmioglu Polat S (2023) Evaluation of candidemia in children at a university hospital: a retrospective cohort. Mycoses 66: 367–377. doi: 10.1111/myc.13564.
26. Xiao G, Liao W, Zhang Y, Luo X, Zhang C, Li G, Yang Y, Xu Y (2020) Analysis of fungal bloodstream infection in intensive care units in the Meizhou region of China: species distribution and resistance and the risk factors for patient mortality. BMC Infect Dis 20: 599. doi: 10.1186/s12879-020-05291-1.
27. Keighley C, Pope A L, Marriott D, Chen SC, Slavin MA, Australia, New Zealand Mycoses Interest Group (2023) Time-to-positivity in bloodstream infection for *Candida* species as a prognostic marker for mortality. Med Mycol 61: myad028. doi: 10.1093/mmy/myad028.
28. Vaquero-Herrero MP, Ragozzino S, Iriart X, Castano-Romero F, Sailler L, Sanchez-Gonzalez R, Cassaing S, Charpentier E, Berry A, Carbonell C, Siller-Ruiz M, Garcia-Garcia I, Soriano A, Marcos M, Ternavasio-de la Vega HG (2020) *Candida* bloodstream infection in patients with systemic autoimmune diseases. Med Mal Infect 50: 372–376. doi: 10.1016/j.medmal.2020.01.014.
29. Rajendran R, Sherry L, Nile CJ, Sherriff A, Johnson EM, Hanson MF, Williams C, Munro CA, Jones BJ, Ramage G (2016) Biofilm formation is a risk factor for mortality in patients with *Candida albicans* bloodstream infection-Scotland, 2012-2013. Clin Microbiol Infect 22: 87–93. doi: 10.1016/j.cmi.2015.09.018.

Annex – Supplementary Items

Supplementary Table 1. The distribution of fungal species by gender.

Species	Male (n)	Female (n)	*p* value
C. albicans (n = 52)	37	15	****0.002**
C. parapsilosis (n = 55)	29	26	0.686
C. tropicalis (n = 21)	12	9	0.513
C. Glabrata (n = 11)	5	6	0.763
C. dubliniensis (n = 11)	8	3	0.227

****$p < 0.01$** represents statistically significant differences. *C. albicans*: *Candida albicans*; *C. parapsilosis*: *Candida parapsilosis*; *C. tropicalis*: *Candida tropicalis*; *C. glabrata*: *Candida glabrata*; *C. dubliniensis*: *Candida dubliniensis*.