Antimicrobial Resistance & Infection Control

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Risk factors and outcome for bloodstream infections due to fluconazole-resistant *Candida parapsilosis*: a 22-year single-center retrospective study

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Abstract

Candidemia ranks among the top causes of nosocomial bloodstream infections, significantly increasing hospital stays and costs. Rapid and effective empirical antifungal therapy is crucial. The *Candida parapsilosis* species complex, the second most common cause of candidemia, has shown rising fluconazole resistance globally and in our country. Additionally, echinocandins exhibit higher minimum inhibitory concentrations (MICs) for *C. parapsilosis*, complicating empirical treatment decisions. This retrospective study analyzed 173 *C. parapsilosis* candidemia cases over 22 years in a tertiary care hospital. We compared 88 fluconazole non-susceptible (minimum inhibitory concentration [MIC] = 4 µg/mL: susceptible dose dependent; MIC ≥ 8 µg/ml resistant) and 85 fluconazole susceptible cases, examining demographics, clinical characteristics, risk factors, and 28-day mortality. Independent risk factors for fluconazole non-susceptibilty included age ≥ 66 years ($p = 0.016$), central venous catheter use ($p < 0.001$), total parenteral nutrition ($p = 0.003$), and colostomy ($p = 0.049$). Fluconazole non-susceptible cases had lower microbiological cure rates and higher mortality. Mortality in this group was independently associated with microbiological cure failure ($p < 0.001$). This study highlights the importance of identifying risk factors to estimate the likelihood of resistant pathogens, initiating targeted antifungal therapy, and providing individualized management. Monitoring local resistance patterns is essential to guide empirical therapy. Further multicenter research is needed to validate findings and optimize treatment for fluconazole resistant candidemia.

Clinical trial number: Not applicable.

Keywords *C. parapsilosis*, Fluconazole resistance, Risk factors

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Introduction

Candida species are the first among the opportunistic fungi that cause disease in humans and cause 10–15% of nosocomial infections [1]. Invasive candidiasis is most common type of nosocomial candidal infections [2]. The most common risk factors for the development of invasive candida infection are the use of broad-spectrum antibiotics and immunosuppressive agents, central venous catheter (CVC), implant and prosthetic device use, total parenteral nutrition (TPN), presence of neutropenia and kidney transplantation [3, 4]. More than 50% of nosocomial candidiasis are caused by *C. albicans* [5]. On the other hand, non-albicans *Candida species* have increased in recent years [6, 7, 8, 9]. This is due to the factors like advancements in laboratory techniques, increasing number of immunocompromised patients, long-term use of corticosteroids and immunosuppressive drugs, prolonged hospital stays, the use of advanced life support systems, and varying levels of resistance to commonly used antifungal drugs [10, 11]. The importance of this situation is probability of resistance to commonly used antifungal drugs in non-albicans *Candida species*. Studies have shown that candidemia increases the length of hospital stay and medical costs, and mortality [12]. Rapid and effective empirical antifungal therapy is a priority in managing candidemia. In studies conducted in our country, *C. parapsilosis* species complex was generally isolated in the second rank [13, 14]. In the "Infectious Diseases Society of America" (IDSA) guideline, it is recommended to start fluconazole (BIII) primarily for the treatment of *C. parapsilosis* and to continue echinocandin if the clinical and microbiological response is obtained [15]. Increasing fluconazole resistance in *C. parapsilosis* leaves clinicians in a problematic situation in choosing empirical treatment. On the other hand, echinocandins have higher minimum inhibitory concentration (MIC) values for *C. parapsilosis* than for other *Candida species* [16]. *C. parapsilosis* is a species with low virulence that carries an inherent mutation in the fks gene, the target of echinocandins. Despite exhibiting higher MIC values for echinocandins than *C. albicans*, it remains clinically susceptible to these agents. However, it is associated with an increased risk of persistent and relapsing infections in humans [17]. Therefore, knowing the epidemiology of *Candida species* in your location and the risk factors in the patient is important in choosing empiric treatment. *C. parapsilosis* species complex is our hospital's second most common *Candida species* isolated from blood samples [18]. In a previous study conducted in our country, fluconazole resistance was higher than expected [19]. The aim of our study was to retrospectively analyze fluconazole non susceptible *C. parapsilosis* bloodstream infections followed in a tertiary university hospital over 22 years to define the epidemiological characteristics of patients, candidemia risk factors, prognostic factors affecting mortality and to guide the selection of appropriate empirical treatment.

Materials and methods

Our retrospective case-control study is conducted in a tertiary care hospital with 1,000 beds, serving a large population. The study included 88 patients below and above 18 years old who were hospitalized in various wards and intensive care units between 1997 and 2019. These patients were diagnosed with candidemia, with blood cultures revealing *C. parapsilosis* species complex isolates that were fluconazole non-susceptible (MIC = 4 µg/mL susceptible dose dependent; MIC ≥ 8 µg/mL resistant). As a control group, 85 patients with blood cultures showing fluconazole-susceptible *C. parapsilosis* isolates were included. Risk factors for fluconazole resistant *C. parapsilosis* and various clinical parameters, including 28 day mortality, were analyzed to evaluate treatment outcomes between fluconazole resistant and susceptible *C. parapsilosis* groups. The patients were in oncology, hematology, general surgery, pulmonary diseases, thoracic surgery, pediatrics, neurosurgery, plastic and reconstructive surgery, neurology, anesthesiology and reanimation, general surgery, pediatric intensive care units. The control group was randomly selected from inpatients hospitalized in similar clinics and from whom fluconazole-susceptible *C. parapsilosis* was isolated from blood cultures. The eighty-five patients in the control group were matched with patients with demographic characteristics, underlying diseases, and risk factors similar to those in the case group.

Nosocomial candidemia cases were defined using the Centers for Disease Control and Prevention (CDC) criteria [20]. Only a patient's first episode of candidemia was included in the study; other episodes were excluded.

The data of the patients were obtained from the hospital information management system. Epidemiological features such as gender, age, length of hospital stay, TPN use, chemotherapy treatment, hospitalization history, invasive procedures such as a urinary catheter, nephrostomy catheter, CVC, colostomy, comorbidities and underlying diseases, last 90 daily use of antibiotics, accompanying microbiological growths and antifungal agents used in treatment were examined a risk factors. Antifungals and antibiotics used, if any, before the diagnosis of candidemia were recorded. Antibiotic use for at least 48 h within 90 days of the diagnosis was considered antibiotic use. Patients with a neutrophil count below 500/mm^3 were considered as neutropenic [21]. Microbiological cure was defined as two negative blood cultures on two consecutive days [22].

Antifungal susceptibility testing was routinely performed on all *C. parapsilosis* species complex isolated

from their blood cultures of hospitalized patients. *C. parapsilosis* species complex isolates grown in blood cultures (BACTEC-FX: Becton-Dickinson, Sparks, MD, USA) during the study period were identified by germ tube test, morphology on cornmeal tween 80 and chromogenic culture media, and using biochemical prophile (API ID 32 C; BioMérieux, France). Antifungal susceptibility testing was performed using the microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. According to the CLSIM27M44S document, strains with a minimum inhibitory concentration MIC ≥ 4 µg/ml were considered non susceptible (MIC = 4 µg/ml susceptible dose dependent; MIC ≥ 8 µg/ml resistant) to fluconazole [23, 24]. Although CLSI states a value of 4 µg/ml as dose-dependently susceptible, studies have shown that resistance begins at this MIC value and that resistance genes are present. Therefore, in this study, all isolates ≥ 4 µg/ml were expressed as resistant to fluconazole [25, 26].

Ethical considerations

The study was designed and conducted in accordance with the guidelines outlined in the World Medical Association Declaration of Helsinki. This study has been approved by the ethical committee of Bursa Uludağ University Faculty of Medicine review board (Approval No.: 2020-10/15, Dated: 2020/07–10), which serves as the Institutional Review Board (IRB) for our institution. To safeguard patients' privacy and confidentiality, their medical records were anonymized and de-identified. The research team maintained no direct contact or follow-up with the patients. Given the retrospective observational nature of the study, where data collection occurred after patients' discharge or death, and given that no patient identifiers were accessed, the IRB waived the need for informed consent. Human ethics and consent to participate declarations: not applicable. This study is a retrospective analysis and does not fall under the definition of a clinical trial. Clinical trial number: not applicable.

Statistical analysis

Compliance of the variables to normal distribution was evaluated by Shapiro-Wilk tests. Continuous variables were expressed as median (minimum-maximum). Mann-Whitney U test was used to compare continuous variables between groups. Categoric variables were expressed in frequency and percent; Pearson's chi-square and Fisher's exact tests were used to compare groups. The Bonferroni test was used as a multiple comparison test where appropriate. Binary logistic regression analysis determined the independent risk factors for 28 day mortality. The variables were included in a logistic regression model forwardly to determine risk factors. The variables that were found to be significant were considered independent risk factors. The logistic regression model was significant ($p < 0.001$). Statistical analyses were carried out by using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and values of $p < 0.05$ were considered statistically significant.

Results

The annual trends of fluconazole-resistant and fluconazole-susceptible *C. parapsilosis* bloodstream infections in our hospital are illustrated in Fig. 1, highlighting the fluctuations in resistance rates over time. Throughout the study period, the number of resistant cases remained relatively low during the initial years but exhibited a pronounced increase after 2016, peaking in 2018. In contrast, the number of susceptible cases displayed greater variability, with a significant rise noted in 2006 and a gradual decline in subsequent years.

Our study aimed to identify the risk factors and outcomes associated with fluconazole resistant *C. parapsilosis* candidemia compared to fluconazole-susceptible candidemia infections. We found several significant differences between the case and control groups. The demographic features, underlying diseases, risk factors for candidemia, and prognosis of the patients are shown in Table 1. Patients with fluconazole resistant *C. parapsilosis* were older and more likely to have underlying hematological malignancy, gastrointestinal malignancy, cardiovascular disease, recent abdominal surgery, and indwelling devices like central catheters. Most patients in both groups were admitted to the ward (88.6% vs. 85.9%), with no significant difference in Intensive care unit admissions ($p = 0.652$). These patients also had a history of more frequent hospitalizations. Fluconazole resistant *C. parapsilosis* was associated with significantly lower microbiological cure rates (81.8% vs. 93.1%) and higher 28-day mortality (21.5% vs. 8.2%) compared to the susceptible isolates (Table 1).

In univariate analysis, age ≥ 66 years, hypertension, hematological malignancy, gastrointestinal malignancy, cardiovascular disease, recent abdominal surgery, presence of a central venous catheter, total parenteral nutrition, colostomy, and prior hospitalization were associated with fluconazole resistance (Table 2). However, multivariate logistic regression analysis identified age ≥ 66 years ($p = 0.016$, OR: 2.342, 95% CI: 1.500–3.660), central venous catheter ($p < 0.001$, OR: 27.825, 95% CI: 7.150–108.288), TPN ($p = 0.003$, OR: 3.889, 95% CI:1.590–9.512), and colostomy ($p = 0.049$, OR: 4.373, 95% CI:1.008–18.963) as independent risk factors significantly associated with fluconazole resistant *C. parapsilosis* candidemia (Table 2).

The majority of fluconazole resistant isolates were treated with fluconazole (61.4%), however there was

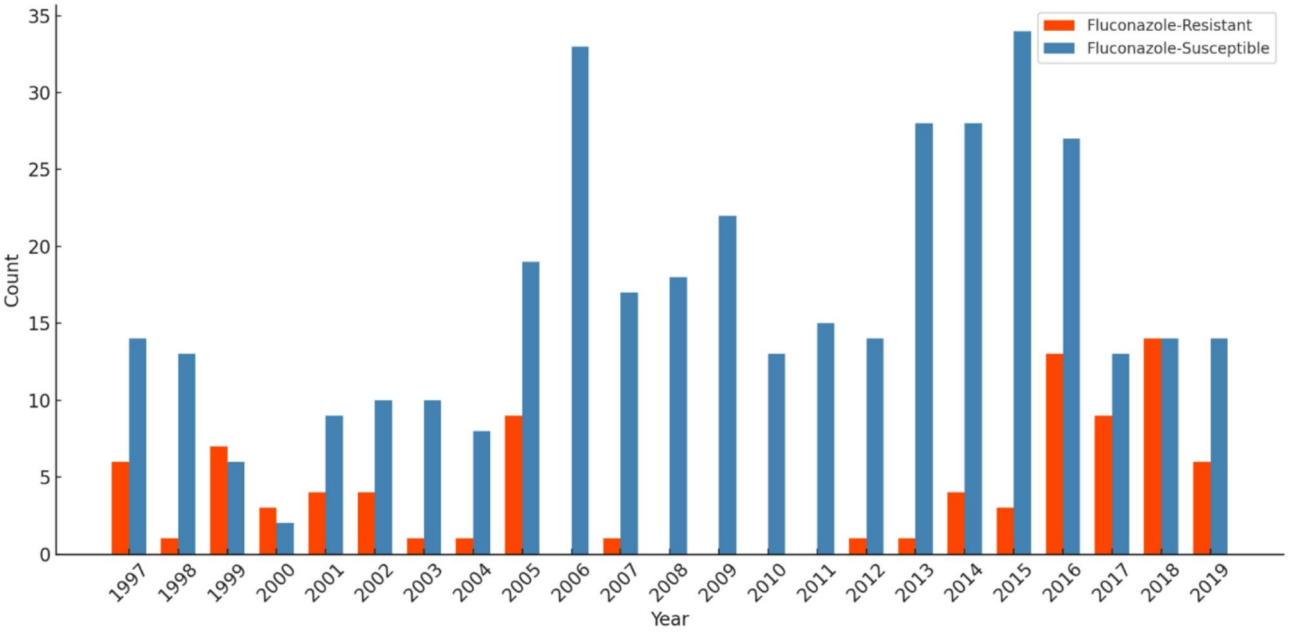

Fig. 1 The annual trends of fluconazole-resistant and fluconazole-susceptible *Candida parapsilosis* bloodstream infections in our hospital

increased use of second-line agents compared to the susceptible group (Table 3). Specifically, a greater proportion of fluconazole resistant isolates were treated with echinocandins (25% vs. 18.8%) and liposomal amphotericin B (10.2% vs. 7.1%) compared to the fluconazole-susceptible isolates. Statistical analysis showed no significant differences in the distribution of antifungal agents between the two groups ($p = 0.384$, chi-square test).

Table 4 summarizes the risk factors associated with mortality in cases of fluconazole resistant *Candida parapsilosis* candidemia. The death group was more likely to have underlying hematological malignancies, solid organ malignancies, and gastrointestinal diseases; however, these differences did not reach statistical significance. The removal of central venous catheters was considered a potential protective factor, as it was less frequently observed in the deceased group. Nevertheless, this observation lacked statistical significance in both univariate and multivariate analyses.

Invasive procedures, including TPN and urinary catheter use, demonstrated no significant differences between survivors and the deceased group. Univariate analysis identified microbiological cure as significantly associated with survival ($p < 0.001$). Furthermore, multivariate analysis confirmed microbiological cure as an independent protective factor against mortality ($p < 0.001$, OR: 0.031, 95% CI: 0.006–0.163). Although colostomy was observed more frequently in the survivor group, it did not retain statistical significance in either univariate or multivariate analysis (Table 5).

Discussion

This retrospective study found several significant differences between fluconazole resistant and fluconazole-susceptible *C. parapsilosis* candidemia cases over a 22-year period at a single center. During the period covered by this study, fluconazole-resistant isolates were encountered every year except for the middle five-year gap. Although we did not demonstrate this in this study, we think that fluconazole-resistant C. *parapsilosis* isolates spread clonally and we can assume that there was no such clonal spread in our hospital in the middle period. However, the increase in fluconazole resistance in our hospital in recent years was unquestionably demonstrated in this study. According to recent literature, there has been a notable increase in the frequency of infections caused by azole-resistant *C. parapsilosis* [27]. This rise is believed to be significantly influenced by global and regional outbreaks, as well as the pharmacological pressures applied during treatment [27, 28]. This situation may particularly trigger resistance development in patients receiving fluconazole treatment or prophylaxis.

Patients with fluconazole resistant *C. parapsilosis* candidemia were significantly older than those with susceptible infections (median 62.5 (1–91) years vs. 55 (1–85) years). Older individuals are more likely to have healthcare exposures, devices, and comorbidities associated with drug-resistant infections [29]. Immunosenescence also impairs antifungal host defenses [30]. In a study, there was close to significance in detecting fluconazole resistant *Candida* in individuals over 65 years of age [31]. In our study, age ≥ 66 years ($p = 0.016$, OR: 2.342, 95% CI: 1.500–3.660) was identified as a risk factor for

Table 1 Demographic characteristics, risk factors, and prognosis of patients with fluconazole resistant and fluconazole susceptible *C. parapsilosis*

	Fluconazole resistant *C. parapsilosis* (*n* = 88)	Fluconazole sensitive *C. parapsilosis* (*n* = 85)	*p* value
Demographic features			
Age years, median (IQR)	62.5 (1–91)	55 (1–85)	**0.027**
Age 0–- 1 years, n (%)	6 (6.8%)	8 (9.4%)	
Age 2–- 17 years, n (%)	9 (10.2%)	10 (11.8%)	**0.115**
Age 18–- 65 years, n (%)	36 (40.9%)	46 (54.1%)	
Age ≥ 66 years, n (%)	37 (42.0%)	21 (24.7%)	
Sex male, n (%)	50 (56.8%)	46 (51.1%)	0.721
Hospital Admitted			
Ward	78 (88.6%)	73 (85.9%)	0.652
Intensive Care Unit	10 (11.4%)	12 (14.1%)	0.652
Patients' underlying diseases			
Diabetes Mellitus, n (%)	10 (11.4%)	10 (11.8%)	0.934
Hypertension, n (%)	6 (6.8%)	16 (18.8%)	**0.018**
Asthma/COPD, n (%)	5 (5.7%)	4 (4.7%)	1.000
Hematological malignancy, n (%)	17 (19.3%)	6 (7.1%)	**0.018**
Solid organ malignancy, n (%)	9 (10.2%)	6 (7.1%)	0.459
GI malignancy, n (%)	42 (47.7%)	21 (24.7%)	**0.002**
GI Diseases, n (%)	23 (26.1%)	12 (14.1%)	**0.049**
CVD, n (%)	21 (23.9%)	10 (11.8%)	**0.038**
Hepatobiliary system diseases, n (%)	7 (8.0%)	5 (5.9%)	0.592
CNS Diseases, n (%)	13 (14.8%)	5 (5.9%)	0.056
Abdominal Operation, n (%)	38 (43.2%)	23 (27.1%)	**0.026**
Burn, n (%)	11 (12.5%)	6 (7.1%)	0.229
Invasive Procedures			
CVC, n (%)	85 (96.6%)	38 (44.7%)	**< 0.001**
TPN, n (%)	70 (79.5%)	38 (44.7%)	**< 0.001**
TPN duration (> 3 days), n (%)	51 (72.9%)	21 (55.3%)	0.064
Urinary Catheter, n (%)	76 (86.4%)	58 (68.2%)	**0.004**
Nephrostomy Catheter, n (%)	4 (4.5%)	3 (3.5%)	1.000
Colostomy, n (%)	22 (25.0%)	10 (11.8%)	**0.025**
History of hospitalization in the last 3 months, n (%)	56 (63.6%)	38 (44.7%)	**0.012**
Length of stay in hospital, median (IQR)	11 (0–94)	13 (0–37)	0.259
Chemotherapy treatment, n (%)	26 (29.5%)	17 (20.0%)	0.146
Neutropenia, n (%)	14 (15.9%)	13 (15.3%)	0.911
Sepsis-1, n (%)	9 (10.2%)	5 (5.9%)	0.295
Antimicrobial exposure in the last 90 days			
Carbapenem, n (%)	58 (65.9%)	60 (70.6%)	0.509
Glycopeptide, n (%)	44 (50.0%)	44 (51.8%)	0.816
^{4t}h generation cephalosporin, n (%)	12 (13.6%)	12 (14.1%)	0.927
^{3r}d generation cephalosporin, n (%)	2 (2.3%)	4 (4.7%)	0.438
Fluoroquinolone, n (%)	7 (8.0%)	5 (5.9%)	0.592
Aminoglycoside, n (%)	17 (19.3%)	15 (17.6%)	0.777
Colistin, n (%)	11 (12.5%)	10 (11.8%)	0.882
Tigecycline, n (%)	4 (4.5%)	4 (4.7%)	1.000
Anti-pseudomonal penicillin, n (%)	8 (9.1%)	3 (3.5%)	0.134
Linezolid, n (%)	10 (11.4%)	10 (11.8%)	0.934
Daptomycin, n (%)	5 (5.7%)	1 (1.2%)	0.211
Trimethoprim-sulfomethoxazole, n (%)	8 (9.1%)	9 (10.6%)	0.741
Fluconazole, n (%)	20 (22.7%)	19 (22.4%)	0.953
Prognosis			
Death, n (%)	19 (21.5%)	7 (8.2%)	**0.014**

Table 1 (continued)

	Fluconazole resistant *C. parapsilosis* (*n* = 88)	Fluconazole sensitive *C. parapsilosis* (*n* = 85)	*p* value
Microbiological Cure, n (%)	72 (81.8%)	82 (93.1)	**0.002**
Microbiological Curing Time days, median (IQR)	3 (1–33)	2 (1–12)	0.476

COPD: Chronic obstructive pulmonary disease, GI: Gastrointestinal, CVD: Cardiovascular disease, CNS: Central nervous system, CVC: Central venous catheter, TPN: Total parenteral nutrition, CRP: C-reactive protein

Table 2 Identified risk factors for fluconazole resistant *C. parapsilosis* candidemia

	Univariate Analysis				Multivariate Analysis			
	p	OR	95% CI for OR		*p*	OR	95% CI for OR	
Age ≥ 66 years	**0.017**	**2.211**	**1.155**	**4.234**	**0.016**	**2.342**	**1.500**	**3.660**
Hypertension	**0.023**	**0.316**	**0.117**	**0.850**	0.231	0.376	0.076	1.861
Hematological malignancy	**0.022**	**3.153**	**1.178**	**8.437**	0.122	2.942	0.750	11.541
GI malignancy	**0.002**	**2.783**	**1.458**	**5.311**	0.065	2.426	0.946	6.220
CVD	**0.042**	**2.351**	**1.033**	**5.348**	0.126	2.683	0.758	9.498
Abdominal Operation	**0.028**	**2.049**	**1.083**	**3.877**	0.394	0.593	0.178	1.975
CVC	**< 0.001**	**35.044**	**10.261**	**119.679**	**< 0.001**	**27.825**	**7.150**	**108.288**
TPN	**< 0.001**	**4.810**	**2.457**	**9.415**	**0.003**	**3.889**	**1.590**	**9.512**
Colostomy	**0.028**	**2.500**	**1.104**	**5.662**	**0.049**	**4.373**	**1.008**	**18.963**
History of hospitalization in the last three months	**0.013**	**2.164**	**1.177**	**3.981**	0.057	2.460	0.974	6.216

GI: Gastrointestinal, CVD: Cardiovascular disease, CVC: Central venous catheter, TPN: Total parenteral nutrition

Table 3 Comparison of antifungal agents used in the treatment of fluconazole resistant and fluconazole-susceptible *Candida parapsilosis* candidemia

Antifungal	Fluconazole resistant *C. parapsilosis* (*n* = 88)	Fluconazole sensitive *C. parapsilosis* (*n* = 85)	*p* value
Fluconazole	54 (61.4%)	62 (72.9%)	0.384
Echinocandin	22 (25.0%)	16 (18.8%)	
Liposomal amphotericin B	9 (10.2%)	6 (7.1%)	
Voriconazole	3 (3.4%)	1 (1.2%)	

fluconazole resistant *C. parapsilosis* candidemia. Monitoring local epidemiology is important, as fluconazole resistance predominantly affects different age groups depending on setting.

Underlying CVD was more prevalent in the fluconazole resistant group ($p = 0.042$, OR: 2.351 95% CI: 1.033–5.348). CVD often necessitates implants and interventions that breach integumentary barriers to infection. Structural heart defects and valvular disease promote seeding of *Candida* to the bloodstream [32]. Immunomodulatory heart failure therapies like steroids may also impair fungal clearance.

Hypertension was less common in the fluconazole resistant group ($p = 0.023$, OR: 0.316 95% CI: 0.117–0.850). The reason for this discrepancy is unclear. It may relate to unmeasured confounding variables or the broad inclusion criterion of any degree of hypertension. Additional studies controlling for hypertension severity and treatment are warranted.

GI malignancy was significantly more common in the fluconazole resistant *C. parapsilosis* group (47.7% vs. 24.7% OR 2.783). This likely reflects shared risk factors for colonization and infection with resistant isolates. GI tumors cause mucosal disruption, immune dysfunction, and microbial translocation all of which may predispose to disseminated candidiasis [33]. Chemotherapy exacerbates these effects, as well as directly impairing neutrophil function critical for fungal clearance [34]. In a study on candidemia in patients with solid tumors, those with GI tumors were the most common, and *C. parapsilosis* was the leading cause of the fungal infections in them [35]. Resistant isolates may originate from fungal overgrowth and biofilms in the tumor microenvironment and disrupted gut mucosa [36]. GI procedures like colorectal surgery have also been identified as risk factors for fluconazole resistance [37]. Breaches in gut mucosal barriers enable translocation of colonizing resistant strains. This was likely a contributing factor in this study population given the higher rate of recent abdominal surgery.

In our study, the use of urinary catheters was observed more frequently in fluconazole resistant cases (86.4% compared to 68.2%). The relationship between urinary catheterization and fluconazole resistant *C. parapsilosis* infections is a growing concern in clinical practice. *C. parapsilosis* is well-known for its capacity to form biofilms on medical devices, including urinary catheters, and is frequently implicated in nosocomial infections, particularly among patients undergoing long-term

Table 4 Risk factors for mortality in fluconazole resistant *C. parapsilosis*

	Survive (*n* = 69)	Death (*n* = 19)	*p* value
Demographic features			
Age years, median (IQR)	62.00 (1–- 91)	64.00 (1–- 80)	0.883
Sex male, n (%)	38 (55.1%)	12 (63.2%)	0.607
Patients' underlying diseases			
Diabetes Mellitus, n (%)	7 (10.1%)	3 (15.8%)	0.445
Hypertension, n (%)	3 (4.3%)	3 (15.7%)	0.294
Hematological malignancy, n (%)	11 (15.9%)	6 (31.6%)	0.186
Solid organ malignancy, n (%)	6 (8.7%)	3 (15.8%)	0.399
GI malignancy, n (%)	33 (47.8%)	9 (47.4%)	1.000
GI Diseases, n (%)	16 (23.2%)	7 (36.8%)	0.249
Hepatobiliary system diseases, n (%)	7 (10.1%)	0 (0.0%)	0.338
CVD, n (%)	17 (24.6%)	4 (21.1%)	1.000
CNS Diseases, n (%)	11 (15.9%)	2 (10.5%)	0.726
Burn, n (%)	7 (10.1%)	4 (21.1%)	0.242
Abdominal Operation, n (%)	32 (46.4%)	6 (31.6%)	0.302
Asthma/COPD, n (%)	3 (4.3%)	2 (10.5%)	0.294
Sepsis-1, n (%)	6 (8.6%)	3 (15.7%)	0.196
History of hospitalization in the last 3 months, n (%)	44 (63.8%)	12 (63.2%)	1.000
Chemotherapy treatment, n (%)	18 (26.1%)	8 (42.1%)	0.255
Antimicrobial exposure in the last 90 days			
Carbapenem, n (%)	45 (65.2%)	13 (68.4%)	1.000
Glycopeptide, n (%)	36 (52.2%)	8 (42.1%)	0.605
^{4t}h generation cephalosporin, n (%)	11 (15.9%)	1 (5.3%)	0.449
^{3r}d generation cephalosporin, n (%)	1 (1.4%)	1 (5.3%)	0.387
Fluoroquinolone, n (%)	6 (8.7%)	1 (5.3%)	1.000
Aminoglycoside, n (%)	13 (18.8%)	4 (21.1%)	1.000
Colistin, n (%)	8 (11.6%)	3 (15.8%)	0.697
Tigecycline, n (%)	4 (5.8%)	0 (0.0%)	0.573
Anti-pseudomonal penicillin, n (%)	6 (8.7%)	2 (10.5%)	1.000
Linezolid, n (%)	7 (10.1%)	3 (15.8%)	0.445
Daptomycin, n (%)	5 (7.2%)	0 (0.0%)	0.581
Trimethoprim-sulfomethoxazole, n (%)	5 (7.2%)	3 (15.8%)	0.362
Fluconazole, n (%)	13 (18.8%)	7 (36.8%)	0.124
Invasive Procedures			
CVC, n (%)	66 (95.7%)	19 (100.0%)	1.000
TPN, n (%)	53 (76.8%)	17 (89.5%)	0.339
Urinary Catheter, n (%)	59 (85.5%)	17 (89.5%)	1.000
Nephrostomy Catheter, n (%)	3 (4.3%)	1 (5.3%)	1.000
Colostomy, n (%)	21 (30.4%)	1 (5.3%)	0.054
CVC Remove, n (%)	60 (87.0%)	13 (68.4%)	0.065
Microbiological Cure, n (%)	64 (92.8%)	8 (42.1%)	**< 0.001**

COPD: Chronic obstructive pulmonary disease, GI: Gastrointestinal, CVD: Cardiovascular disease, CNS: Central nervous system, CVC: Central venous catheter, TPN: Total parenteral nutrition, CRP: C-reactive protein

Table 5 Univariate and multivariate analysis of risk factors for mortality in fluconazole resistant *C. parapsilosis*

	Univariate Analysis				Multivariate Analysis			
	p	OR	95% CI for OR		*p*	OR	95% CI for OR	
Colostomy	0.054	0.126	0.015	1.014	0.155	0.057	0.004	0.693
ALT (IU/L)	0.124	3.153	1.178	8.437	0.122	2.942	0.750	11.541
CVC Remove	0.065	0.325	0.098	1.073	0.505	0.564	0.105	3.030
Microbiological Cure	**< 0.001**	**0.056**	**0.015**	**0.205**	**< 0.001**	**0.031**	**0.006**	**0.163**

catheterization [38]. Catheter manipulations can further compromise mucosal barriers, enhancing microbial translocation. Moreover, urinary catheter use has been strongly correlated with increased rates of fluconazole resistant infections, especially among critically ill patients in intensive care units (ICUs). This association likely stems from a combination of prolonged catheterization, which supports *C. parapsilosis* colonization, and the selective pressure created by antifungal prophylactic therapies [39, 40].

In our study, the presence of CVC was found to be the strongest independent risk factor for fluconazole resistance ($p < 0.001$, OR 27.825, 95%CI 7.150–108.288), which is similar to the study in the literature on fluconazole resistance in candidemia [41]. The biofilm-forming ability of *C. parapsilosis* likely underlies its predilection to cause catheter-related infections [42]. One study found that all patients with *C. parapsilosis* bloodstream infection had central venous access and 77.7% of the isolates were resistant to fluconazole [43]. Biofilms may provide a reservoir for antifungal resistance development [44]. Beyond biofilms, the foreign body presence and frequent manipulation of CVCs provide a nidus for infection. The use of CVCs likely selects for translocation of gut colonizers like *C. parapsilosis*, which has specific adhesins and secreted lipases promoting endothelial adherence and tissue invasion [45, 46].

We found that TPN use was an independent predictor of fluconazole resistance ($p < 0.003$, OR 3.889, 95%CI 1.590–9.512). Lipid emulsions in TPN enhance *Candida* growth and biofilm formation [47]. TPN also alters gut microbiota and immunity, increasing susceptibility to disseminated candidiasis [48]. Lipid emulsions may be particularly problematic. Medium-chain triglycerides in TPN formulations provide a preferential carbon source for *Candida* species [49]. Beyond enriching the microenvironment, TPN results in intestinal villi atrophy and disruption of gut immunity, likely increasing susceptibility to translocation of *Candida* [50].

Presence of a colostomy was uniquely associated with fluconazole resistance ($p = 0.049$, OR 4.373, 95%CI 1.008–18.963). This association may, at least in part, be attributable to the underlying clinical conditions necessitating colostomy, such as gastrointestinal malignancies or other severe intra-abdominal pathologies that often require extensive surgical intervention. These patients may be subject to prolonged hospitalization, broad-spectrum antimicrobial use, and repeated exposure to healthcare environments, all of which are known risk factors for the selection and persistence of resistant Candida species. Moreover, colostomy-related alterations in the gut microbiota and mucosal immunity may further facilitate colonization and hematogenous dissemination of resistant strains [51]. Further prospective studies are warranted to substantiate and clarify this observed association.

Fluconazole resistant *C. parapsilosis* patients in our study were more likely to have been hospitalized in the previous 3 months (63.6% vs. 44.7% $p = 0.013$, OR 2.164 95%CI 1.777–3.981). This fits with the known associations between healthcare exposure, colonization pressure, and drug-resistant infections [52]. Prolonged hospital stays allow greater *Candida* acquisition, while increased use of CVCs, antibiotics, chemotherapy, and other invasive procedures promote selection of resistant subpopulations [53].

Several risk factors for fluconazole resistant *C. parapsilosis* candidemia were identified in our analysis, including the presence of a central venous catheter, total parenteral nutrition, and colostomy. These factors appeared to confer independent hazard for developing this condition. While literature specifically examining risk factors for fluconazole resistant *C. parapsilosis* candidemia remains limited, a study found diabetes mellitus to be the sole independent risk factor associated with candidemia due to fluconazole resistant *C. parapsilosis* strains [54]. More comprehensive multinational investigations are warranted to confirm these findings and elucidate additional risk factors that may predispose individuals to developing candidemia caused by fluconazole resistant isolates. Elucidating the risk factors for fluconazole resistance in *C. parapsilosis* will be imperative for developing optimal prevention and treatment strategies for this emerging nosocomial pathogen.

The more frequent use of echinocandins in fluconazole resistant *C. parapsilosis* cases compared to fluconazole-susceptible cases in our study (25.0% vs. 18.8%) is probably related to clinicians' suspicion of fluconazole resistance in these patients. Updated guidelines recommend echinocandins as first-line empiric therapy for seriously ill patients with suspected fluconazole resistant invasive candidiasis [15].

In our study, fluconazole resistant isolates were significantly associated with higher 28 day mortality rates (21.5% vs. 8.2%, $p = 0.018$, OR 3.068, 95% CI 1.217–7.739). Fungaemia caused by *Candida parapsilosis* has been reported to have a mortality rate of approximately 25%, which is lower compared to *Candida albicans* fungemia. However, the mortality rate may increase substantially in patients with malignancies or those with cardiovascular prosthetic devices [55]. A previous study reported a 30-day mortality rate of 32.4% for *C. parapsilosis* [56]. Additionally, the study conducted in Japan identified APACHE II score > 25 and retained cardiovascular prosthetic materials (prosthetic valve or graft) as a significant risk factor for mortality in fluconazole resistant *C. parapsilosis* candidemia [55]. In our study, after adjusting for confounding factors, microbiological cure emerged as

the sole independent predictor of survival ($p < 0.001$, OR 0.031, 95% CI 0.006–0.163).

Our study has several limitations. First, this is a single-center retrospective analysis, which may not capture the broader spectrum of patients seen in other institutions or regions. Selection bias could have affected the results as data from only patients with available medical records were included. Additionally, while we have identified statistically significant associations, causality cannot be inferred from this type of study design. There may also be other confounding variables that were not accounted for in our analysis. Furthermore, the evolution of clinical practices and diagnostics over the 22-year study period may have introduced some variability in the data. For example, caspofungin was introduced in our hospital in 2014, leading to differences in treatment approaches and intensive care management practices. Importantly, in the fluconazole-resistant *C. parapsilosis* group, the majority of patients received fluconazole despite the organism's resistance. This therapeutic mismatch may have contributed to the lower microbiological cure rates observed in this group and could represent a confounding factor in evaluating the true impact of resistance on outcomes. Therefore, the possibility that treatment failure was due to inappropriate antifungal choice rather than resistance alone should be considered when interpreting these results.

In conclusion, fluconazole-resistant *C. parapsilosis* candidemia poses significant challenges for clinicians due to its association with increased morbidity and mortality. Our study identified several significant risk factors, including the presence of a central venous catheter, the requirement for total parenteral nutrition, and having a colostomy. Compared to previous studies, our research offers a unique perspective by spanning a 22-year period and including a substantial patient cohort of 173 cases, allowing for robust and meaningful analysis. Colostomy was identified as a potential risk factor, a finding not previously emphasized in the literature. This association may reflect underlying conditions such as gastrointestinal malignancies and repeated intra-abdominal surgeries, which are known to influence microbiota integrity and antimicrobial exposure. Further studies are warranted to validate this observation and clarify its clinical implications. The higher mortality observed in patients with fluconazole-resistant infections underscores the importance of selecting effective antifungal therapies based on local epidemiologic and resistance data, and of considering individual patient risk factors when making treatment decisions. Further multicenter, prospective studies with standardized data collection and unified diagnostic criteria are warranted to confirm our findings and minimize inter-institutional variability. Additionally, international collaborative efforts involving larger patient cohorts would be valuable in identifying regional differences in resistance patterns and optimizing evidence-based strategies to improve outcomes in patients with fluconazole-resistant *C. parapsilosis* candidemia.

Acknowledgements
Not applicable.

Author contributions
CS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review and editing. EK: Conceptualization, Data curation, Formal analysis, Investigation, Writing—review and editing. BE: Formal analysis, Writing—review and editing. SA: Data curation, Formal analysis. GÖ: Data curation, Formal analysis. HA: Data curation, Formal analysis. YH: Data curation, Formal analysis. EY: Data curation, Formal analysis. HA: Data curation, Formal analysis, Review and editing. All authors have read and agreed to the published version of the manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study has been approved by the ethical committee of Bursa Uludağ University Faculty of Medicine review board (Approval No.: 2020-10/15, Dated: 2020/07–10), which serves as the Institutional Review Board (IRB) for our institution. No written informed consent was provided to patients as all data were analyzed anonymously after a deidentification process.

Human Ethics
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 23 January 2025 / Accepted: 22 April 2025
Published online: 14 May 2025

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