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Evaluation of species distribution, risk factors, and treatment modalities of *Candida* infections in the intensive care unit of a tertiary care center in Western Turkey

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Abstract

Introduction: *Candida* species are increasingly recognized as significant nosocomial pathogens. In patients hospitalized in the intensive care units (ICUs), the risk of candidemia is particularly high due to the coexistence of multiple risk factors.

Objective: In this study, we investigated the distribution of *Candida species*, antifungal susceptibility, risk factors, and mortality in ICU patients with nosocomial *Candida* infections.

Methods: This retrospective study included 63 adult patients with candidemia hospitalized in the ICU between January 2021 and March 2023. Demographic, clinical, and laboratory data were analyzed. Statistical analysis was performed using the Chi-square test, Mann–Whitney *U* test, and logistic regression.

Results: Non-albicans *Candida* (NAC) species accounted for 61.9% of all isolates, with *Candida parapsilosis* (42.8%) being the most common. Gastrointestinal surgery significantly increased the risk of NAC infection (p=0.038). Higher serum albumin levels were associated with a reduced risk of mortality (odds ratio [OR]: 0.86, 95% confidence interval [CI]: 0.77–0.97, p=0.013), and elevated urea levels were associated with an increased risk of mortality (OR: 1.023, 95% CI: 1.008–1.038, p=0.002). All of the 16 tested isolates were susceptible to anidulafungin, while 66.6% of *C. parapsilosis* isolates were resistant to fluconazole. The overall mortality rate was 66.7%.

Conclusions: NAC species should be considered in empirical treatment strategies, particularly for patients hospitalized in ICUs where this species is prevalent and for those with a history of gastrointestinal surgery. Low albumin and elevated urea may serve as potential predictors of mortality and should be carefully monitored. Echinocandins remain the most appropriate empirical agents given the high fluconazole resistance observed among *C. parapsilosis* isolates.

Keywords: *Candida parapsilosis*; Candidemia; Risk factors; Antifungal susceptibility

1. Introduction

Candida species have emerged as increasingly important agents of nosocomial infections. Especially in patients hospitalized in the intensive care unit (ICU), the risk of candidemia is relatively heightened due to the coexistence of many risk factors. The prolonged survival of ICU patients concomitantly increases the risk of candidemia, which is further amplified by the widespread use of antineoplastic and immunosuppressive therapies, increased frequency of surgical procedures, solid organ and hematopoietic stem cell transplantation, total parenteral nutrition, and broad-spectrum antibiotic exposure.[1]

The epidemiological landscape of candidemia is not uniform; the frequency and incidence of causative *Candida* species vary substantially between institutions due to differences in local risk factor profiles. These species also demonstrate distinct clinical tendencies: while *Candida albicans* is typically associated with catheter-related bloodstream infections and intra-abdominal abscesses, *Candida parapsilosis* is frequently linked to parenteral nutrition and invasive devices, and *Candida glabrata* or *Candida krusei* are more common in elderly or immunocompromised hosts with prior azole exposure.[2-4]

Globally, *Candida* species rank among the most prevalent causative agents of bloodstream infections in the ICU settings.[5] In the United States, they represent the fourth most common cause of healthcare-associated infections and the second leading cause of healthcare-associated bloodstream infections.[6] Although over 15 *Candida* species can cause human disease, more than 95% of invasive infections are attributed to five primary pathogens: *C. albicans*, *C. glabrata*, *Candida tropicalis*, *C. parapsilosis*, and *C. krusei*. Notably, while *C. albicans* has historically been the dominant species, the incidence of non-albicans *Candida* (NAC) species has progressively increased over the past decade, now accounting for over 50% of cases in many regions.[5,6]

This shift toward NAC species is also evident in Turkey. Recent multicenter surveillance studies have demonstrated that ICU-associated candidemia cases attributed to non-albicans *Candida* species have now surpassed those caused by *C. albicans*, with *C. parapsilosis* emerging as the predominant isolate in several tertiary care hospitals.[7-9] Although no nationwide candidemia registry has yet been established, these multicenter data collectively provide the most comprehensive insight into the national epidemiology, highlighting the predominance of NAC species and the growing clinical relevance of *C. parapsilosis* in Turkey. Similar epidemiological patterns have also been reported in other Mediterranean regions, reflecting the impact of local infection-control practices and antifungal resistance dynamics.

Advances in antifungal therapy and refinement of treatment algorithms have broadened therapeutic options, and timely initiation of appropriate antifungal agents has been consistently shown to improve survival outcomes in *Candida* infections.[10] Consequently, treatment success hinges on a comprehensive understanding of the infection source, disease severity, patient comorbidities, and the local epidemiology of predominant *Candida* species and their antifungal susceptibility profiles.[5] The inherent heterogeneity of these data necessitates that individual centers maintain their own surveillance programs to effectively guide infection management and therapeutic decisions.

Although several studies have investigated candidemia in Turkey, most were conducted before the COVID-19 pandemic and before the emergence of azole-resistant *C. parapsilosis* strains. The present study provides updated, post-pandemic, region-specific data from Western Turkey, focusing on changes in species distribution, antifungal susceptibility patterns, and mortality-associated risk factors among ICU patients. By separately evaluating risk factors for NAC infections and correlating antifungal resistance profiles with clinical outcomes, this study contributes novel and clinically relevant insights that may guide empirical antifungal therapy in tertiary care ICUs.

The primary aim of our study was to evaluate the distribution of *Candida* species, antifungal susceptibility patterns, risk factors, and mortality rates associated with nosocomial *Candida* infections in adult patients hospitalized in the ICU of a tertiary care center.

2. Materials and methods

2.1. Materials and instruments

This was a single-center, retrospective study involving patients over 18 years old who were hospitalized in the Anesthesiology and Reanimation ICU of a tertiary care teaching hospital between January 01, 2021, and March 15, 2023. Candidemia was defined as the isolation of *Candida* spp. from at least one blood culture. The study included patients with at least one blood culture positive for *Candida* species obtained ≥48 h after hospital admission, in the presence of compatible clinical findings (fever, hypotension, or sepsis). Episodes representing colonization or contamination, rather than true infection, were excluded from the study.

Blood cultures were monitored using the BACTEC FX TOP automated system (Becton Dickinson, Sparks, MD, USA). Positive samples were examined through Gram staining and cultured on blood agar (bioMérieux, Marcy-l'Étoile, France) and Eosin Methylene Blue agar (Oxoid, Hampshire, UK), incubated at 37°C for 24–48 h.

Cultures showing opaque, cream-colored colonies with yeast odor underwent Gram staining and germ tube tests, and were subcultured on Sabouraud Dextrose Agar (Oxoid, Hampshire, UK) for identification and antifungal susceptibility testing.

Species identification was performed using the PHOENIX 100 automated system (Becton Dickinson, Sparks, MD, USA). Molecular confirmation methods such as internal transcribed spacer (ITS) or 18S rRNA sequencing were not available during the study period; therefore, species identification was conducted using conventional phenotypic and biochemical approaches, which are widely used in clinical microbiology laboratories.

Antifungal susceptibility was assessed using the gradient E-test method (Bioanalyse, Turkey). Results were interpreted according to CLSI guidelines.[11-13]

2.2. Methods

Demographic data, underlying diseases, candidemia risk factors, disease severity (APACHE II scores), laboratory parameters, *Candida* species distribution, antifungal susceptibility patterns, treatments, durations, and their effects on mortality were analyzed.

Risk factors of candidemia included the presence of central venous catheters (CVCs), administration of total parenteral nutrition, utilization of mechanical ventilation, corticosteroid therapy, a history of gastrointestinal surgical interventions, documented *Candida* colonization, burn injuries, and prior exposure to broad-spectrum antimicrobial agents. Broad-spectrum antimicrobials refer to agents with activity against a wide range of Gram-positive and Gram-negative bacteria, such as third- and fourth-generation cephalosporins, carbapenems, fluoroquinolones, and penicillin–beta-lactamase inhibitor combinations. Total parenteral nutrition was defined as glucose–amino acid–lipid emulsion via CVC for ≥48 h.

Fluconazole was administered to clinically stable patients without prior azole exposure, while echinocandins were given to others.

Hematological and biochemical biomarkers were calculated as follows: the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio were obtained from complete blood counts, while the C-reactive protein-to-albumin ratio (CAR) was derived from biochemical parameters. These biomarkers were assessed for their impact on mortality.

2.3. Ethical approval and consent to participate

The study was approved by the Clinical Research Ethics Committee of University of Health Sciences İzmir Bozyaka Training and Research Hospital (decision no.: 2023/46). Due to the retrospective design of this study, the requirement for informed consent was waived.

2.4. Statistical analysis

Data analysis was performed using IBM SPSS version 26.0. The Kolmogorov–Smirnov test was employed to assess the normality of data distribution. The arithmetic mean, standard deviation, minimum, and maximum values of descriptive data were calculated. Differences of normally distributed data between two groups were analyzed using an independent samples *t*-test, whereas differences among more than two independent groups were evaluated using one-way analysis of variance. The Mann–Whitney *U* test was used to analyze differences of non-normally distributed data between two independent groups, whereas the Kruskal–Wallis H test was opted for analyzing differences among more than two groups. Categorical variables were analyzed using Fisher's exact and Chi-square tests. To identify independent predictors of mortality, variables with $p<0.10$ in the univariate analysis were entered into a multivariate logistic regression model. The assumptions of logistic regression were verified: multicollinearity was assessed based on the variance inflation factor (VIF) and tolerance values, ensuring no variable exceeded the standard thresholds (VIF < 5; tolerance > 0.2). The results are reported as odds ratios (OR) with 95% confidence intervals (CI). A $p<0.05$ was considered statistically significant.

3. Results

The study included 63 patients, with 65.1% male and 34.9% female. The mean age was 60.98 ± 19.27 years, and the median was 63.00 years (IQR: 48–77). In this study, NAC species were the leading cause of candidemia among patients in the ICU (61.9%), with *C. parapsilosis* being the most common species (42.8%). Demographic, medical history, clinical characteristics, and mortality rates were compared between *C. albicans* and NAC groups (Table 1).

Analysis of candidemia risk factors revealed that 96.8% of the patients (n = 61) had CVCs, 95.2% (n = 60) used broad-spectrum antibiotics, 65.1% (n = 41) were on mechanical ventilation, and 44.4% (n = 28) received total parenteral nutrition. The mean duration of antibiotic use before candidemia was 17.22 ± 12.83 days, with piperacillin-tazobactam and moxifloxacin being the most common. Previous gastrointestinal surgery significantly increased the risk of NAC infection (p=0.038). No significant differences in risk factors were found between living and deceased patients (Table 2).

Candida species isolated as causative agents are shown in Figure 1. NAC was predominant (61.9%), followed by

Table 1. Demographic characteristics of patients with non-albicans *Candida* versus *Candida albicans* infections

Variables	All patients (*n*=63)	Non-albicans *Candida* isolates (*n*=39)	*Candida albicans* isolates (*n*=24)	*p*
Age (years), M (IQR)	63.00 (48.00–77.00)	62 (44–77)	66 (57–76)	0.410[a]
Length of hospitalization (days), M (IQR)	40 (18–69)	45 (23–72)	34 (16.50–60.75)	0.330[a]
Length of hospitalization before candidemia (days), M (IQR)	16 (10.75–30.75)	19 (10–36)	14.50 (11.00–20.50)	0.230[a]
APACHE II Score, mean±SD	25.32±10.59	26.52±8.46	23.35±13.41	0.290[b]
Gender				
Female	22 (34.9)	12 (30.8)	10 (41.7)	0.540[c]
Male	41 (65.1)	27 (69.2)	14 (58.3)	
Presence of comorbidities	44 (69.8)	27 (69.2)	18 (75)	0.830[c]
Hypertension	26 (41.3)	18 (46.2)	8 (33.3)	0.450[c]
Diabetes mellitus	15 (23.8)	7 (17.9)	8 (33.3)	0.270[c]
CAD	9 (14.3)	6 (15.4)	3 (12.5)	0.530[c]
Malignancy	8 (12.7)	6 (15.4)	2 (8.3)	0.410[c]
Cerebrovascular event	6 (9.5)	5 (12.8)	1 (4.2)	0.250[c]
COPD	4 (6.3)	4 (10.3)	0 (0)	0.100[c]
CRF	3 (4.7)	2 (5.1)	1 (4.2)	0.860[c]
Antifungal treatment				
Yes	44 (69.8)	30 (76.9)	14 (58.3)	0.200[c]
No	19 (30.2)	9 (23.1)	10 (41.7)	
Antifungal treatment				
Fluconazole	16 (25.4)	10 (25.6)	6 (25)	1[c]
Caspofungin	25 (39.7)	17 (43.6)	8 (33.3)	0.580[c]
Amphotericin B	3 (4.8)	3 (7.7)	0 (0)	0.160[c]
Antifungal use before candidemia				
Yes	4 (6.3)	2 (5.1)	2 (8.3)	0.610[c]
No	59 (93.7)	37 (94.9)	22 (91.7)	
Duration of treatment (days), M (IQR)	13 (0–22)	13 (0–22)	11 (0–22)	0.860[a]
Mortality	42 (66.7)	25 (64.1)	17 (70.8)	0.780[c]

Notes: Data are expressed as count and percentage, unless otherwise indicated. [a]Mann–Whitney *U* test, [b]Student's *t*-test, [c]Chi-square test.
Abbreviations: CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CRF: Chronic renal failure; M (IQR): Median (interquartile range); SD: Standard deviation.

Table 2. Association of clinical risk factors with *Candida* species distribution and patient mortality outcomes

Risk factors	*Candida* species distribution			Patient mortality outcomes		
	Non-albicans *Candida*, *n* (%)	*Candida albicans*, *n* (%)	*p*[a]	Non-survivors, *n* (%)	Survivors, *n* (%)	*p*[a]
Central venous catheter placement	37 (60.7)	24 (39.3)	0.52	41 (97.6)	20 (95.2)	0.610
Parenteral nutrition	19 (67.9)	9 (32.1)	0.54	19 (45.2)	9 (42.9)	1
Use of broad-spectrum antibiotic	38 (63.3)	22 (36.7)	0.29	40 (95.2)	20 (95.2)	1
Previous gastrointestinal surgery	7 (100)	0 (0)	0.028	4 (9.5)	3 (14.3)	0.570
Steroid use	8 (47.1)	9 (52.9)	0.23	14 (33.3)	3 (14.3)	0.190
Presence of *Candida* colonization	17 (53.1)	15 (46.9)	0.23	20 (47.6)	12 (57.1)	0.650
Mechanical ventilation	23 (56.1)	18 (43.9)	0.30	29 (69)	12 (57.1)	0.510
Burn	4 (57.1)	3 (42.9)	0.78	3 (7.1)	4 (19)	0.150

Note: [a]Chi-square test.

C. parapsilosis (42.9%), *C. albicans* (38.1%), *C. tropicalis* (12.7%), *C. glabrata* (4.8%), and *C. krusei* (1.6%). The mean hospitalization duration before candidemia onset was 23.29 ± 21.18 days. Hospitalization duration varied by species: 47.00 ± 35.20 days for *C. krusei*, 68.37 ± 52.10 days for *C. parapsilosis,* and 46.42 ± 43.69 days for *C. albicans*. There was no significant difference in hospitalization length between NAC and *C. albicans* groups (p=0.33), but those infected by *C. parapsilosis* experienced a significantly prolonged hospital stay (p=0.011).

Regarding antifungal use, 93.7% of the patients (n = 59) had never received antifungal treatment before the onset of candidemia. The mean duration of antifungal treatment was 12.27 ± 12.27 days. Antifungals used in the present study included fluconazole (25.4%), caspofungin (39%), and amphotericin B (4.8%). Antifungal susceptibility tests were performed on 16 patients, and the results showed 100% susceptibility to anidulafungin and 68.7% to fluconazole. Notably, fluconazole resistance was found in 66.6% of *C. parapsilosis* strains, while anidulafungin resistance was absent (Table 3).

Mortality occurred in 66.7% of the patients. Compared to the surviving patients, the deceased patients exhibited lower levels of monocyte (p=0.047), platelet (p=0.017), albumin (p=0.007), and alanine transaminase (p=0.034), as well as higher levels of urea (p=0.002) and CAR (p=0.049).

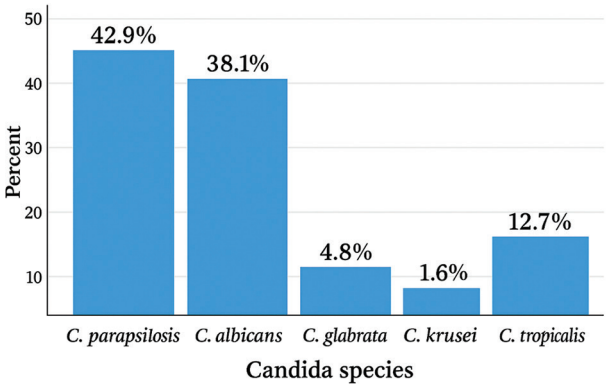

Figure 1. Distribution of *Candida* species of patients

Deceased patients in this cohort also received less treatment (p=0.041) and had shorter treatment durations (p=0.041) (Table 4). In multivariate analysis, albumin and urea were significant. The ideal cut-off values for predicting mortality were albumin <29.5 g/L (sensitivity 52.4%, specificity 95.2%) and urea >80 mg/dL (sensitivity 52.4%, specificity 90.5%). Higher serum albumin levels were associated with a reduced risk of mortality (OR: 0.86, 95% CI: 0.77–0.97, p=0.013), and elevated urea levels were associated with an increased risk of mortality (OR: 1.023, 95% CI: 1.008–1.038, p=0.002).

4. Discussion

Our findings confirm that NAC species, particularly *C. parapsilosis*, constitute the predominant etiology of candidemia in the ICU. This observation is consistent with an evolving epidemiological trend documented in recent Turkish and broader Mediterranean studies. The shift toward NAC species is largely driven by factors prevalent in critical care settings, such as the extensive use of invasive devices, total parenteral nutrition, and the propensity of certain species, notably *C. parapsilosis*, for biofilm formation on medical equipment. The predominance of *C. parapsilosis* in our cohort can likely be attributed to its strong affinity for forming biofilms on intravascular catheters and other medical devices, as well as its potential for horizontal transmission via healthcare workers' hands. These biological characteristics facilitate persistence in ICU environments and may explain its regional predominance despite stringent infection-control measures. The known capacity of *C. parapsilosis* to form biofilms on catheters, coupled with its association with nosocomial transmission via hands, underscores the critical need for stringent infection control protocols and meticulous catheter management in curbing its spread.

The geographical and temporal variation in *Candida* species distribution is evident when comparing our data with international and national reports. A recent study conducted in France identified *C. albicans* (44%) as the most frequent bloodstream isolate, followed by *C. glabrata* (22%) and *C. parapsilosis* (13%),[14] and another study also

Table 3. Antifungal susceptibility test results of *Candida* isolates

Species (n)	Fluconazole-susceptible, n (%)	Fluconazole-resistant, n (%)	Anidulafungin-susceptible, n (%)	Anidulafungin-resistant, n (%)
Candida albicans (n=5)	5 (100)	0 (0)	5 (100)	0 (0)
Candida parapsilosis (n=6)	2 (33.3)	4 (66.7)	6 (100)	0 (0)
Candida tropicalis (n=4)	4 (100)	0 (0)	4 (100)	0 (0)
Candida glabrata (n=1)	0 (0)	1 (100)	1 (100)	0 (0)
Non-*albicans Candida* (n=11)	6 (54.5)	5 (45.5)	11 (100)	0 (0)

Table 4. Demographic characteristics of survivors versus non-survivors

Variables	All patients (*n*=63)	Non-survivors (*n*=42) (66.7%)	Survivors (*n*=21) (33.3%)	*p*
Age (years), M (IQR)	63.00 (48.00–77.00)	66.00 (57.00–78.00)	61.00 (32.00–70.50	0.07[a]
Length of hospitalization (days), M (IQR)	40 (18–69)	41.00 (14.00–63.50)	40.00 (31.00–105.50)	0.12[a]
Length of hospitalization before candidemia (days), M (IQR)	16 (10.75–30.75)	17.00 (9.50–33.00)	14.00 (10.50–27.50)	0.67[a]
APACHE II Score, mean±SD	25.32±10.59	26.17±10.49	23.53±10.89	0.40[b]
Gender				0.45[c]
Male	41 (65.1)	26 (61.9)	15 (71.4)	
Female	22 (34.9)	16 (38.1)	6 (28.6)	
Concomitant disease				0.07[c]
Yes	44 (69.8)	33 (78.6)	12 (57.1)	
No	19 (30.2)	9 (21.4)	9 (42.9)	
Leukocytes (/μL), M (IQR)	12690 (8820–17000)	12510 (8820–16282)	12820 (8960–19025)	0.49[a]
Neutrophils (/μL), M (IQR)	10210 (6780–14860)	9625 (6407–13425)	11180 (7090–16080)	0.33[a]
Lymphocytes (/μL), M (IQR)	1040 (650–1630)	975 (622.5–1665,5)	1300 (690–1755)	0.39[a]
Monocytes (/μL), M (IQR)	480 (260–860)	405 (207–837)	600 (440–1125)	0.047[a]
Platelets (/μL), M (IQR)	250,000 (127,000–395,000)	213,500 (96,000–333,250)	297,000 (241,000–453,500)	0.017[a]
Hemoglobin (g/dL), M (IQR)	8.9 (8.1–10.1)	8.80 (7.87–9.60)	9.70 (8.65–10.45)	0.090[a]
Procalcitonin (μg/L), M (IQR)	0.70 (0.30–1.80)	0.64 (0.30–2.20)	0.70 (0.24–1.61)	0.330[a]
CRP (mg/L), mean±SD	173.76±101.40	184.34±98.41	152.60±106.37	0.240[b]
AST (IU/L), M (IQR)	28 (16–56)	29.00 (15.50–56.25)	27 (16–56)	0.960[a]
ALT (IU/L), M (IQR)	26 (10–42)	21.00 (7.00–37.25)	37 (21–64)	0.034[a]
Total bilirubin (mg/dL), M (IQR)	0.60 (0.40–0.97)	0.66 (0.35–0.98)	0.50 (0.40–0.73)	0.470[a]
Urea (mg/dL), M (IQR)	58 (33–113)	82.00 (39.25–139.25)	46 (28–61)	0.002[a]
Creatine (mg/dL), M (IQR)	0.84 (0.4–1.7)	1.10 (0.47–1.82)	0.50 (0.40–1.19)	0.060[a]
Albumin (g/L), mean±SD	22.99±5.51	21.70±5.27	25.59±5.14	0.007[b]
Lactate (mmol/L), M (IQR)	1.8 (1.5–2.6)	1.8 (1.5–2.8)	1.90 (1.55–2.25)	0.770[a]
NLR, M (IQR)	9.94 (5.23–15.89)	10.23 (4.44–16.47)	9.68 (6.28–14.55)	0.740[a]
PLR, M (IQR)	228.51 (152.46–355.74)	215.84 (106.78–337.68)	286.79 (196.82–413.85)	0.060[a]
LMR, M (IQR)	2.23 (1.29–4.02)	2.73 (1.41–4.87)	1.73 (1.07–2.50)	0.100[a]
CAR, mean±SD	8.33±6.04	9.38±6.51	6.22±4.37	0.049[b]
Antifungal treatment				0.041[c]
Yes	44 (69.8)	26 (61.9)	18 (85.7)	
No	19 (30.2)	16 (38.1)	3 (14.3)	
Antifungal				
Fluconazole	16 (25.4)	8 (19)	8 (38.1)	0.180[c]
Caspofungin	25 (39.7)	15 (35.7)	10 (47.6)	0.520[c]
Amphotericin B	3 (4.8)	3 (7.1)	3 (14.3)	0.200[c]
Duration of treatment (days), M (IQR)	13 (0–22)	5.50 (0–19.75)	16.00 (9.50–25.00)	0.041[a]

Notes: Data are expressed as count and percentage, unless otherwise indicated. [a]Mann–Whitney *U* test, [b]Student's *t*-test, [c]Chi-square test.
Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CAR: CRP-to-albumin ratio; CRP: C-reactive protein; M (IQR): Median (interquartile range); NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SD: Standard deviation.

reported a similar predominance of *C. albicans*.[15] Our results from this study align more closely with a shifting pattern observed in the region under investigation. This shift becomes apparent on reviewing the longitudinal data, with analysis by Kocabaş *et al.*[7] pointed out *C. albicans* (47.3%) as the most common species, followed by

C. parapsilosis (25.5%) from 2014 to 2019. However, more recent investigations, including those by Kerget *et al.*[16] (2018–2019), have documented a clear emergence of *C. parapsilosis* as the leading causative agent, accounting for 43.3% of candidemia cases occurring in the ICU. In parallel, our study identified NAC species in 61.9% of cases, with *C. parapsilosis* (42.8%) slightly surpassing *C. albicans* (38.1%). This collective evidence from our center and other contemporary national studies indicates that while *C. albicans* remains the most common agent globally,[17] *C. parapsilosis* has now become the predominant species in our national context. To better contextualize our findings within national and international data, a comparative summary of recent studies on ICU-associated candidemia is presented in Table 5. This table illustrates variations in case numbers, predominant species, and mortality rates across different settings, highlighting their regional shifts concerning the NAC species.

Since most patients hospitalized in the ICU are associated with important risk factors, including mechanical ventilation, CVC, and broad-spectrum antibiotic use, hospitalization in the ICU is regarded as a risk factor of candidemia.[11] The profile of our patient cohort underscores the high-risk environment of the ICU for candidemia development. As established in the literature, ICU hospitalization is a significant risk factor in itself, which is largely attributable to the aggregate burden of interventions such as mechanical ventilation, CVC placement, and broad-spectrum antibiotic exposure.[18] This paradigm was reflected in our study population, where a substantial majority of patients were exposed to these key risk factors: CVC was present in 19.30% of patients, 8.86% received total parenteral nutrition, 18.89% were administered broad-spectrum antibiotics, and 12.97% underwent mechanical ventilation. Beyond these general risks, the specific predisposing factors appear to vary according to the causative *Candida* species.

A growing body of evidence suggests that NAC-associated candidemia is linked to distinct clinical antecedents. A study comparing NAC and *C. albicans* risk factors found that fluconazole use and CVC placement were two important risk factors for NAC-associated candidemia, which was more common in patients with gastrointestinal surgical intervention.[19] In the study of Dimopoulos *et al.*,[20] candidiasis, CVC placement, and steroid use were identified as risk factors for NAC-associated candidemia. In another study, previous gastrointestinal surgical intervention and recent systemic antifungal use were found to increase the risk for NAC infections in ICU patients.[21] In our study, previous gastrointestinal surgical intervention was found to significantly increase the risk for NAC infections. The use of broad-spectrum antibiotics is another important condition that increases the incidence of these infections.[22] Broad-spectrum antibiotics alter the natural intestinal and urinary microbiota, leading to an overgrowth of *Candida*. In a study conducted in Japan, the effect of an antibiotic management program on the control of candidemia was evaluated. Fifty patients who received broad-spectrum antipseudomonal antibiotics (carbapenems, tazobactam/piperacillin, and cefepime) and intravenous quinolone therapy for more than 7 days, had positive blood cultures, and were unresponsive to treatment were included in the study. Restricted usage of broad-spectrum antibiotics (especially carbapenems) has been found to reduce the incidence of hospital-acquired candidemia.[23] Our data align with this finding, indicating a prolonged mean antibiotic exposure of 17.22 ± 12.83 days before candidemia onset, with piperacillin/tazobactam

Table 5. Comparison of major studies on ICU-associated candidemia

Study (year)	Country/Setting	Number of cases	Predominant species	NAC prevalence (%)	Mortality rate (%)	Key findings/Notes
Kutlu *et al.* (2022)[8]	Turkey (11 tertiary care ICUs)	326	*Candida parapsilosis*	61.9	48.5	NAC species dominant; *Candida parapsilosis* most frequent.
Aydin *et al.* (2022)[9]	Turkey (multicenter, 7 years)	245	*Candida parapsilosis*	63.2	46.7	Increasing fluconazole resistance among *Candida parapsilosis*.
Pfaller and Diekema (2007)[17]	Global surveillance	>4,000	*Candida albicans*	45–55	40–50	Regional variation; *Candida glabrata* more common in elderly and immunocompromised.
Toda *et al.*, 2019[18]	United States (Population-based active surveillance, 4 sites)	3,492	*Candida albicans, Candida glabrata*	61	25	*Candida glabrata* second most common; highest mortality observed among older adults and ICU patients.
The present study (2023)	Turkey (Western, single ICU)	63	*Candida parapsilosis*	61.9	66.7	High NAC rate; *C. parapsilosis* dominant; fluconazole resistance 66.6%.

Notes: Data adapted from other papers.[8,9,17,18]
Abbreviations: ICU: Intensive care unit; NAC: Non-albicans *Candida*.

(PTZ) and moxifloxacin being the most frequently administered agents.

The particular risk posed by PTZ is well-established, with literature reporting a fourfold increase in candidemia incidence, notably for *C. glabrata* and *C. krusei*.[24] This effect was attributed to its potent anti-anaerobic activity and the enhanced colonization of the gastrointestinal system by *Candida* species resulting from its high local concentration.[24] A significant increase in oral and rectal colonization was shown on the seventh day of PTZ treatment.[25] Considering the impact of quinolones on candidemia, gastrointestinal *Candida* colonization rose slightly with a treatment regime consisting of ciprofloxacin, norfloxacin, and ofloxacin, compared to a markedly increased colonization with levofloxacin and moxifloxacin.[26,27] Collectively, the evidence confirms that microbiota disruption by specific, high-risk antibiotics is a principal driver of candidemia. Consequently, rigorous antimicrobial stewardship emerges as a cornerstone of prevention. This strategy necessitates the timely discontinuation of therapy on clinical resolution and the avoidance of unnecessary prescriptions, particularly for agents with a marked propensity to induce fungal colonization, such as PTZ and later-generation quinolones.

Monocytes are immune cells that play an important role in host immune response against fungal infections. Detection of fungi by monocytes triggers signaling pathways that directly affect phagocytosis and cytokine production. While monocytes stimulate the inflammatory response through both phagocytosis and cytokine production, they also trigger the adaptive immune system through fungal antigen presentation.[28] In *C. albicans* infection, Dektin-1 and Dektin-2 play a role in the generation of an inflammatory response by triggering cytokine release and phagocytosis from monocytes.[29] In addition, it is remarkable that monocytes can distinguish different morphological forms of fungi by expression of pattern recognition receptors.[30] In various studies, different hematologic parameters have been shown to be associated with mortality in candidemia. Thrombocytopenia,[8] particularly changes in platelet percentage and mean platelet volume,[9] are parameters found to be associated with mortality. Consistent with the literature, our study found that the platelet count was significantly lower in deceased patients than in the living patients. This finding underscores the importance of monocytes in the control of candidemia.

The overall mortality rate observed in our study was 66.7%, a figure that exceeds the rates reported in several national series. This elevated mortality likely reflects the high baseline severity of illness in our cohort, potential delays in the initiation of appropriate antifungal therapy, and a significant burden of underlying comorbidities. Mortality in candidemia is influenced by a complex interplay of the causative *Candida* species, specific risk factors, and the development of organ dysfunction. Our findings that hypoalbuminemia and elevated urea levels were associated with increased mortality align with this concept. These parameters likely function as markers of profound systemic inflammation and organ dysfunction rather than directly modifiable targets, yet they may serve as valuable indicators for early prognostic assessment.

The risk factors we identified are consistent with the broader literature. A prospective multicenter study from Turkey highlighted high Sequential Organ Failure Assessment (SOFA) score, total parenteral nutrition, prior antibiotic use, post-candidemia thrombocytopenia, and renal failure as significant predictors of 30-day mortality, while also underscoring the life-saving importance of timely antifungal treatment and CVC removal.[8] Other national studies have corroborated the mortality risk associated with a high SOFA score, prolonged ICU stay, CVC placement, total parenteral nutrition, broad-spectrum antibiotics use, concurrent bacteremia, and renal replacement therapy.[31,32] Furthermore, a study from China also presented evidence regarding the association of broad-spectrum antibiotic use, hypoalbuminemia, long-term parenteral nutrition, and major surgery with mortality risk.[15]

The consistency of these findings across different studies—including the association of renal impairment with a 2.14-fold higher mortality[33] and the role of hypoalbuminemia as emphasized by Kır and Bahceci[34]—strengthens the validity of our results. Therefore, the high mortality in our cohort can be interpreted as a multifactorial outcome, driven by the aggregate effect of high-risk patient profiles, specific clinical interventions, and the ensuing systemic physiological deterioration.

This study provides a detailed epidemiological overview of candidemia in ICU-hospitalized adult patients; however, its findings should be cautiously interpreted in light of limitations. Although our results provide valuable insights into the epidemiology of ICU-associated candidemia in Western Turkey, these findings should not be generalized to the entire population of the country, as this was a single-center, retrospective study. The epidemiological distribution of *Candida* species may vary substantially among institutions due to differences in patient populations, antifungal stewardship practices, and infection-control measures. Nevertheless, our results are broadly consistent with recent multicenter surveillance studies from Turkey, which similarly reported the predominance of NAC species, particularly *C. parapsilosis*, in tertiary care ICUs.[7-9]

These national data, together with our institutional findings, underscore the ongoing shift in *Candida* species profiles and highlight the importance of maintaining local and regional epidemiological monitoring.

The single-center, retrospective design may limit the generalizability of the results, and the predominance of *C. parapsilosis* in our cohort could reflect local infection control dynamics rather than regional epidemiology. A key constraint is the limited antifungal susceptibility data, with only 16 isolates tested. Consequently, the notably high fluconazole resistance rate observed in *C. parapsilosis* (66.6%), although striking, requires cautious interpretation and validation in larger, multicenter studies.

Only 16 isolates were subjected to antifungal susceptibility analysis in this study, representing a limited subset of the total cohort. While this subset offers valuable preliminary information regarding local resistance trends, the small sample size limits the generalizability of the findings. In particular, the fluconazole resistance rate of 66.6% among *C. parapsilosis* isolates is higher than those reported in most national and international series, possibly reflecting local epidemiological variation, antifungal selection pressure, or sampling bias. Therefore, these data should be interpreted with caution and confirmed through larger, multicenter investigations.

An additional methodological consideration is that species identification was conducted using conventional phenotypic and biochemical methods, as molecular confirmation (*e.g.*, ITS or 18S rRNA sequencing) was not available during the study period.

5. Conclusion

This study provides crucial, region-specific insights into the evolving epidemiology of ICU-associated candidemia in Western Turkey. Our findings confirm the predominance shift toward NAC species, with *C. parapsilosis* emerging as the predominant pathogen. The notably high rate of fluconazole resistance observed among *C. parapsilosis* isolates indicates an evolving local threat that warrants careful review of empirical antifungal treatment protocols. These results strongly support the continued use of echinocandins as first-line therapy and highlight the essential need for antifungal susceptibility testing before treatment de-escalation. However, these findings should be interpreted with caution, given the single-center, retrospective design, limited sample size, and incomplete antifungal susceptibility data, which may introduce selection bias and restrict generalizability. Furthermore, the high mortality observed emphasizes the prognostic significance of biochemical markers such as hypoalbuminemia and elevated urea levels, underscoring the importance of early identification and timely antifungal intervention in critically ill patients. Future multicenter, prospective investigations with larger sample sizes are warranted to validate these results and to guide nationwide antifungal stewardship and infection-control strategies.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

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Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Izmir Bozyaka Training and Research Hospital (date: 29.03.2023; decision no.: 2023/46). The study was conducted in compliance with the principles of Declaration of Helsinki. Due to the retrospective design of this study, the requirement for informed consent was waived.

Consent for publication

Not applicable.

Availability of data

All data analyzed in this study are included within the article.

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