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Candidemia in Turkey demonstrates nationwide predominance of non-albicans *Candida* and *Candida auris* detection

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Title

Candidemia in Turkey demonstrates Nationwide predominance of Non-albicans *Candida* and *Candida auris* Detection

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Abstract

In recent years, evolving patterns in candidemia epidemiology, including increasing proportions of non-*albicans Candida* (NAC) species and the emergence of *Candida auris*, have been reported. We aimed to characterize contemporary candidemia epidemiology in Turkey and to assess the association between guideline adherence and 30-day mortality. In this nationwide retrospective multicenter cohort study, adult patients with blood culture–confirmed candidemia diagnosed between January 2022 and December 2023 in 20 hospitals were included. Species identification was standardized and confirmed using MALDI-TOF MS. A total of 398 candidemia episodes were analyzed. Although *Candida albicans* remained the single most common species (34.7%), NAC species predominated overall (65.3%), mainly driven by *Candida parapsilosis* (26.6%), while *C. auris* accounted for 6.5% of cases and was detected across multiple centers. Crude mortality was 68.3% and 30-day mortality was 56.3%. Failure to remove central venous catheters (CVC) was independently associated with higher 30-day mortality. Kaplan–Meier analysis demonstrated significant differences in 30-day survival across EQUAL *Candida* score categories in the overall candidemia cohort (log-rank p = 0.02) and among patients with CVC-related candidemia cohort (log-rank p = 0.008). Collectively, our findings provide a contemporary nationwide overview of candidemia in Turkey, highlighting the predominance of NAC species, the multicenter detection of *C. auris*, and the clinical importance of early source control.

Keywords: Candidemia; *Candida parapsilosis*; *Candida auris*; Catheters, Indwelling; Epidemiology; Mortality; Non-albicans *Candida*;

Introduction

Candidemia is the fourth most common bloodstream infection among hospitalized patients, and its incidence has been estimated to have doubled worldwide. This rise is largely attributed to the increasing prevalence of

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major predisposing factors, including immunosuppression, invasive medical interventions, broad-spectrum antibiotic use, and improved diagnostic capacity. In addition, the coronavirus disease 2019 (COVID-19) pandemic and the emergence of multidrug-resistant fungi, such as *C. auris*, have raised further concerns regarding the epidemiology of invasive fungal infections. Moreover, despite improvements in treatment strategies, mortality in candidemia remains significant, reaching 65%, often accompanied by prolonged hospitalization and increased costs [1,2].

Although *C. albicans* remains the most frequently isolated species, evolving epidemiological patterns in candidemia have been increasingly reported in recent years, including a shift toward non-albicans *Candida* (NAC) species and the emerging threat of *C. auris* [2–6]. In studies conducted in Turkey, increases in both the incidence of candidemia and the proportion of NAC species have been described, along with a growing number of cases and outbreaks related to *C. auris* since 2020 [7–10]. However, nationwide multicenter data integrating contemporary epidemiological trends and real-world adherence to guideline-based management in Turkey remain limited.

The treatment of candidemia has undergone significant changes over the last decade and has reached a certain level of standardization and several guidelines on its management have been published. Most recently, updated global guidelines developed collaboratively by the European Confederation of Medical Mycology (ECMM), the International Society for Human and Animal Mycology (ISHAM), and the American Society for Microbiology (ASM) in 2025 have provided comprehensive recommendations for the diagnosis and management of candidiasis [11].The European Confederation of Medical Mycology also developed the European Confederation of Medical Mycology Quality of Clinical Candidemia Management (EQUAL) *Candida* score in 2018 to assess adherence to the latest guidelines in both the diagnosis and management of candidemia and to highlight the most important aspects of current recommendations [12]. Quality indicators are scored according to their impact on patient outcomes and the strength of the evidence. Although guidelines are fundamental to evidence-based medicine, they can be difficult to follow in clinical practice and in some cases, the treatment of patients with candidemia may be individualized owing to the geographic variation in pathogens and resistance patterns [4,12,13].

In this study, we aimed to provide a comprehensive nationwide overview of candidemia epidemiology and species distribution in Turkey, with particular attention to the proportion of NAC species and the presence of *C. auris*, and to evaluate the association between adherence to the EQUAL *Candida* score and 30-day mortality.

2. Materials and Methods

Between January 2022 and December 2023, patients aged ≥18 years with candidemia from 20 hospitals located in different provinces of Turkey were included in the study (Supplementary Fig. S1). Approximately 20 consecutive blood culture–proven candidemia isolates from each center were included. Candidemia was defined as the isolation of *Candida* spp. in at least one blood culture bottle drawn peripherally or from a

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central line with clinical symptoms. Catheter-associated candidemia was defined as candidemia occurring in patients with a central venous catheter at the time of bloodstream infection, supported by clinical findings and/or microbiological evidence from peripheral and/or catheter-drawn blood cultures, in the absence of another identifiable source reflecting routine clinical practice in a multicenter setting. The date of candidemia was recorded as the date of blood culture collection. The duration of a candidemia episode was defined as 28 days. Blood culture positivity with the same or different *Candida* species within this period was included in the same episode and considered as a single infection. Blood culture positivity developing in the same patient after 28 days was considered as a different episode of candidemia. An outbreak was defined as the occurrence of two or more epidemiologically related candidemia cases caused by the same *Candida* species occurring close in time within the same center, suggesting possible healthcare-associated transmission. As molecular typing was not routinely available across participating centers, outbreak identification relied on epidemiological assessment by the local infection control teams. In consecutive candidemias included from each center, in case of an outbreak (e.g. *C. auris*-associated outbreak), the first candidemia case was included in the study and other cases were excluded from the study to avoid overrepresentation of clustered cases and potential center-level bias. Cultures with mixed infections (two or more fungal species or fungal species with bacteria) were excluded from the analysis.

Demographic information of the patients, comorbidities, ward they were hospitalized in during candidemia, diagnosis, duration of hospitalization, predisposing conditions [surgical interventions in the last month, presence of sepsis, neutropenia (neutrophil count < 500/mm3), total parenteral nutrition (TPN), steroid administration (1mg/kg/day for >20 days), central venous catheter (CVC), urinary catheter and mechanical ventilation (MV), presence of transplantation, intensive care unit (ICU) stay, COVID-19 during hospitalization, broad-spectrum antibiotic and antifungal treatments in the last month] source of candidemia, type of candida isolated, date of candidemia, EQUAL *Candida* score criteria, fungal diagnostic procedures, antifungal therapy, mortality status were retrospectively evaluated from hospital and microbiology laboratory systems and recorded in the standardized case registration form.

Empirical antifungal treatment was defined as treatment initiated by the physician with suspicion of candidemia or blood culture positivity within 72 hours. Sepsis was defined as a documented clinical diagnosis in medical records at the time of candidemia, based on the attending physician's assessment and consistent with international consensus definitions [14]. COVID-19 positivity is defined as the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in respiratory tract specimens or the positivity of rapid diagnostic tests, along with clinical and radiological findings. Death within the 30 days after candidemia was defined as 30-day mortality.

Compliance with candidemia guidelines was measured with the EQUAL *Candida* score, which consists of criteria from diagnosis, treatment and follow-up [12]. EQUAL *Candida* score criteria can be listed as follows: initial adequate blood culture (40 ml) (3 points), identification of the causative agent at the species level (3 points), antifungal susceptibility test (2 points), echocardiography (1 point), ophthalmoscopy (1 point),

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initiation of treatment with echinocandin (3 points), switch to fluconazole according to the susceptibility test result (2 points), treatment for 14 days following the first negative blood culture (2 points), In the presence of a CVC, catheter removal is within the first 24 hours after diagnosis (3 points), catheter removal is within 24-72 hours after diagnosis (2 points), blood cultures are taken at least once a day during follow-up (2 points). The maximum score using these standards is 22 points and 19 points in the absence of a CVC. In cases involving fluconazole-resistant *Candida* species, two points were given if therapy was switched to voriconazole or if treatment with an echinocandin was continued. Furthermore, patients who died within 14 days of starting treatment were assigned two points.

Clinical *Candida* isolates obtained from participating centers were transported to the Koç University Işbank Center for Infectious Diseases Laboratory in Istanbul. Before the MALDI-TOF MS identification, isolates were cultured on Sabouraud dextrose agar, incubated for 24-48 hours, and purified by a second subculture, consistent with standard *Candida* processing methodology. All isolates were identified by MALDI-TOF MS analyzer EXS 2600 (Zybio Inc., China). Isolates for which spectra failed to reach reliable identification thresholds (e.g, log (score) < 1.7) or produced conflicting results across repeated MALDI-TOF MS analyses were classified as 'undetermined'. As this was a multicenter study, antifungal susceptibility testing was not standardized across centers and was performed according to local routine laboratory methods.

In statistical analyses, each *Candida* isolate was treated as a distinct episode and analysed as an individual case. Patients who died within the first 48 hours were excluded from mortality analyses to minimise early outcome bias. Adherence to the EQUAL *Candida* score was evaluated only in patients who survived for at least seven days, as several score components require adequate follow-up time to be performed, in accordance with guideline-based practice and previous studies. Among patients without CVCs, the EQUAL *Candida* score showed limited discriminatory performance, likely reflecting reduced score variability and ceiling effects. Accordingly, categorical analyses were not undertaken in this subgroup. Categorical variables were expressed as numbers and percentages, and continuous variables as mean ± standard deviation (SD) or median (IQR), as appropriate. Group comparisons between 30-day survivors and non-survivors were performed using the chi-square or Fisher's exact test for categorical variables and the Student's t-test or Mann–Whitney U test for continuous variables. Kaplan–Meier survival curves were generated to evaluate 30-day survival across EQUAL *Candida* score categories, and survival distributions were compared using the log-rank test. Variables associated with mortality in univariate analysis ($p < 0.10$), together with clinically relevant factors, were included in a multivariable Cox proportional hazards model to identify independent predictors of 30-day mortality. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). All analyses were two-sided, with $p < 0.05$ considered statistically significant. Statistical analyses were performed using SPSS 22.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA). The authors used a large language model (ChatGPT, OpenAI) to improve language clarity and readability. All scientific content, data interpretation, and conclusions were independently reviewed and approved by the authors. This multicenter study was conducted

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within the framework of the KLİMİK MİÇG Study Group, a nationwide collaborative infectious diseases and clinical microbiology research network in Turkey.

Results

A total of 406 *Candida* isolates were collected from participating centers during the 24-month study period. After exclusion of six isolates due to bacterial contamination and two due to mixed *Candida* growth, 398 isolates were eligible for analysis. No candidemia cases were excluded due to outbreak clustering during the study period. Three isolates originated from the same patient; therefore, the final cohort comprised 396 patients accounting for 398 candidemia episodes**.** The majority of the patients were male (59%), with a mean age of 63.1 ± 15.5 years.

At the onset of candidemia, 55% of patients were hospitalized in the ICU, and the median length of hospital stay was 40 days. At least one comorbidity was present in 92.7% of patients; most commonly hypertension (47.5%), malignancy (44.5%), chronic kidney disease (41.7%), and diabetes mellitus (34.9%). The most frequent risk factors included urinary catheterization (91.2%), broad-spectrum antibiotic exposure (90.5%), presence of CVCs (84.2%), ICU stay (83.4%), MV (68.8%), and sepsis (66.3%). One hundred fifty-one patients (37.9%) had undergone surgery in the month prior to candidemia; of these, 60 (39.7%) had undergone gastrointestinal surgery.

Central venous catheters were identified as the most common source of candidemia (39.7%). Following the diagnosis, CVCs were removed in 187 of 335 patients (55.8%). Notably, nearly one-third of removals (61/187; 32.6%) occurred within the first 24 hours, while more than half (99/187; 53.0%) were performed between 24 and 72 hours after diagnosis. Endocarditis was diagnosed in 8 of 221 patients (3.8%) who underwent echocardiography, while endophthalmitis was identified in 7 of 155 patients (4.5%) who received ophthalmologic examination.

Echinocandins were the most commonly used agents for empirical antifungal therapy (61.4%), whereas fluconazole was used in 28.9% of cases and the median duration of antifungal treatment was 15 days. The overall crude mortality rate was 68.3%. Detailed demographic and clinical characteristics are summarized in Table 1.

Table 1. Demographic and clinical characteristics and outcomes of patients with candidemia (N=398)

Characteristics	N (%)
Male gender	235 (59)
Age, years, mean ± SD	63.1±15.5
Hospital Unit (at time of candidemia)	
Surgical ward	63 (15.8)
Medical ward	116 (29.1)

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Intensive care unit	219 (55)
Duration of hospital stay, days, median (IQR)	40 (25-72.2)
Comorbidities	369 (92.7)
Diabetes mellitus	139 (34.9)
Hypertension	189 (47.5)
Cardiovascular disease	131(32.9)
Chronic kidney disease	166 (41.7)
Chronic liver disease	8 (2)
Chronic lung disease	64 (16.1)
Malignancy	181 (44.5)
Rheumatologic disease	15 (3.8)
Neurologic disease	68 (17.1)
Other medical conditions*	28 (7)
Risk conditions/factors	
Surgery	151 (37.9)
Gastrointestinal surgery	60 (39.7)
Neurosurgery	31 (20.5)
Other surgeries*	60 (39.7)
Neutropenia (<500/mm3)	16 (4)
Central venous catheter	335 (84.2)
Urinary catheter	363 (91.2)
Total parenteral nutrition	174 (43.7)
Mechanical ventilation	274 (68.8)
Corticosteroid use (1mg/kg/day >20 days)	95 (23.9)
Hemodialysis	65 (16.3)
Transplantation	8 (2)
Prior broad spectrum antibiotics use last month	360 (90.5)
Antifungal prophylaxis use last month	60 (15.1)
Intensive care unit admission during hospitalization	332 (83.4)
Sepsis	264 (66.3)
COVID-19 diagnosis	18 (4.5)
Source of candidemia	
Primary	115 (28.9)
Central venous catheter-related	158 (39.7)
Gastrointestinal	58 (14.6)
Urinary tract	59 (14.8)

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Skin soft tissue	8 (2)
Empirical antifungal therapy	
Echinocandin	244 (61.3)
Fluconazole	115 (28.9)
Voriconazole	4 (1)
Amphotericin B	14 (3.5)
No antifungal treatment	21 (5.3)
Duration of antifungal therapy, days, median (IQR)	15 (6-21)
Overall mortality	272 (68.3)
30-day mortality	224 (56.3)
30-day mortality (excluding ≤48-h deaths) n:365	193 (52.9)

*****endocrinology, urology, human immunodeficiency virus infection, psychiatry, metabolic disorders

Candida albicans was the most commonly isolated species (34.7%), followed by *C. parapsilosis* (26.6%), *Candida glabrata* (14.1%), *Candida tropicalis* (9.8%), *C. auris* (6.5%) which was identified in nine participating centers. Other *Candida* species identified less frequently. NAC species accounted for the majority of isolates. The distribution of *Candida* species is presented in Table 2.

Table 2. Distribution of *Candida* species (N=398)

Candida spp.	**N (%)**
C. albicans	138 (34.7)
C. parapsilosis	106 (26.6)
C. glabrata	56 (14.1)
C. tropicalis	39 (9.8)
C. auris	26 (6.5)
C. krusei	8 (2)
C. lusitaniae	6 (1.5)
Others*	15 (3.8)
Undetermined	4 (1)

***** *C. guillermondii, C. dubliniensis, C. kefyr, C. cerevisiae, C. inconspicua, Wickerhamomyces anomalus, C. orthopsilosis*

Comparisons between survivors and non-survivors, including univariate and multivariable analyses for 30-day mortality, are shown in Table 3. While sex distribution did not differ between the groups, non-survivors were significantly older ($p < 0.001$), more frequently had comorbidities ($p = 0.006$), a history of renal failure ($p = 0.02$), ICU admission ($p < 0.001$), sepsis ($p < 0.001$), MV ($p < 0.001$), and urinary catheterization ($p =$

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0.001). The rate of CVC removal and EQUAL *Candida* scores were significantly lower among non-survivors ($p < 0.001$ and $p = 0.01$, respectively).

Variables that were significant in univariate analyses, together with clinically relevant factors, were subsequently entered into a Cox proportional hazards regression model. The presence of comorbidities (HR 4.45, 95% CI 1.58–12.52; $p = 0.005$) and failure to remove the CVC (HR 1.49, 95% CI 1.06–2.10; $p = 0.02$) emerged as independent predictors of mortality. Although the EQUAL *Candida* score did not reach statistical significance in the multivariable analysis (HR 0.95, 95% CI 0.90–1.00; $p = 0.06$), a trend toward lower mortality was observed with increasing scores.

Neither *C. albicans* nor NAC species were associated with 30-day mortality in univariate analysis, and species distribution was not an independent predictor of mortality in multivariate analysis.

In the univariate analysis, a history of surgery was less common among non-survivors. Among the 151 patients who underwent surgery, the mean age was 60.4 ± 16.1 years, compared with 64.7 ± 15.0 years in the 247 patients who did not undergo surgery. Comorbidities were present in 88% of patients in the surgical group and in 95.5% of those in the non-surgical group.

Empirical echinocandin therapy was commonly used in both survivors and non-survivors, with no significant difference between groups (65.9% vs. 62.9%, $p = 0.55$), and was not associated with 30-day mortality in univariate analysis.

Table 3. Univariate and multivariate analysis of factors associated with 30-day mortality in candidemia patients (n=365)

			Univariate analysis		Multivariate analysis	
	Survivor (n=172)	Non-survivor (n=193)	p	HR (95% CI)	p	HR (95% CI)
Gender, n (%)				1.42		
Male	109 (63.4)	106 (54.9)	0.10	(0.93-2.16)		
Female	63 (36.6)	87 (45.1)				
Age, mean±SD	59.66±16.07	65.52±14.40	**<0.001**		0.52	1 (0.99-1.01)
Hospitalization wards, n (%)			0.06			
1. Surgery	33 (19.2)	26 (13.5)				
2. Internal medicine	57 (33.1)	51 (26.4)				
3. ICU	82 (47.7)	116 (60.1)				
History of surgery, n (%)	74 (43)	61 (31.6)	**0.03**	0.61		

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				(0.39-0.93)		
Comorbidity, n (%)	153 (89)	186 (96.4)	**0.006**	3.30 (1.35-8.05)	**0.005**	4.45 (1.58-12.52)
DM, n (%)	64 (37.2)	66 (34.2)	0.88	0.87 (0.57-1.34)		
HT, n (%)	75 (43.6)	96 (49.7)	0.24	1.28 (0.84-1.93)		
Solid cancer, n (%)	67 (39)	84 (43.5)	0.37	1.20 (0.79-1.83)		
Hemotological malignancy, n (%)	3 (1.7)	11 (5.7)	0.06	3.40 (0.93-12.41)	0.51	1.26 (0.61-2.60)
Cardiovascular disease,n (%)	46 (26.7)	70 (36.3)	0.06	1.55 (0.99-2.43)	0.29	1.21 (0.84-1.73)
Chronic obstructive lung disease, n (%)	29 (16.9)	28 (14.5)	0.53	0.83 (0.47-1.47)		
Kidney failure, n (%)	34 (19.8)	59 (30.6)	**0.02**	1.78 (1.10-2.90)	0.72	1.06 (0.74-1.52)
Dialysis, n (%)	25 (14.5)	36 (18.7)	0.29	1.34 (0.77-2.35)		
Neurological disease, n (%)	32 (18.6)	33 (17.1)	0.70	1.34 (0.52-1.54)		
Chronic liver disease, n (%)	1 (0.6)	6 (3.1)	0.12	5.48 (0.65-46.03)		
Rheumatologic disease, n (%)	3 (1.2)	10 (5.2)	0.08	3.07 (0.83-11.37)		
Neutropenia, n (%)	6 (3.5)	8 (4.1)	0.74	1.19 (0.40-3.52)		
CVC, n (%)	147 (85.5)	161 (83.4)	0.59	0.85 (0.48-1.51)		
Steroid use, n (%)	34 (19.8)	53 (27.5)	0.09	1.53 (0.94-2.51)		
Urinary catheter, n (%)	149 (86.6)	186 (96.4)	**0.001**	4.10 (1.71-9.82)	0.25	1.81 (0.65-5.08)
TPN, n (%)	69 (40.1)	89 (46.6)	0.21	1.30 (0.85-1.97)		
Transplantation, n (%)	3 (1.7)	4 (2.1)	1	1,19		

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				(0.26-5.40)		
ICU stay, n (%)	127 (73.8)	176 (91.2)	**<0.001**	3.66 (2-6.70)	0.23	1.59 (0.74-3.43)
Sepsis n (%)	84 (48.8)	157 (81.3)	**<0.001**	4.56 (2.85-7.30)	0.93	1.01 (0.65-1.58)
MV, n (%)	95 (55.2)	156 (80.8)	**<0.001**	3,41 (2.14-5.45)	0.81	1.07 (0.58-1.96)
Covid-19, n (%)	8 (4.7)	9 (4.7)	1	1 (0.37-2.65)		
Source of candidemia, n (%)			0.79			
Urinary	24 (14)	32 (16.6)				
Intra-abdominal	22 (12.8)	29 (15)				
CVC	72 (41.9)	76 (39.4)				
Primary	49 (28.5)	53 (27.5)				
Skin and soft tissue	5 (2.9)	3 (1.6)				
Candida isolates, n (%)			0.68	1.09 (0.71-1.68)		
C. albicans	58 (33.7)	69 (35.8)				
Non-albicans *Candida*	114 (66.3)	124 (64.2)				
Empirical echinocandin treatment, n (%)	112 (65.9)	117 (62.9)	0.55	0.87		
Cardiac involvement, n (%)	4 (3.8)	3 (3.1)	1	0.80 (0.17-3.70)		
CVC removal, n (%) (for patients with CVC)	105 (73.4)	79 (50.6)	**<0.001**	0.37 (0.22-0.60)	**0.02**	0.66 (0.47-0.93)
EQUAL score, median (IQR)	13.5 (11-16)	13 (10-15)	**0.01**		0.06	0.95 (0.90-1)

Among patients who survived at least seven days after candidemia onset, adherence to selected guideline components differed between survivors and non-survivors. Adequate initial blood culture volume (≥40 mL) was more frequently obtained in survivors than in non-survivors (73% vs. 60.5%, p = 0.02). Removal of the CVCs within 24–72 hours was also significantly more common among survivors (42.6% vs. 29.3%, p = 0.03).

In contrast, species identification and completion of 14 days of antifungal therapy were more frequently observed in non-survivors (p = 0.02 and p = 0.04, respectively). No significant differences were found

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between groups with respect to echocardiography, ophthalmoscopy, echinocandin use, de-escalation, early catheter removal (≤24 hours), or daily follow-up blood cultures.

Median EQUAL *Candida* scores were similar between survivors and non-survivors [13 (IQR 11–17) vs. 13 (IQR 10–15), p = 0.19]. Only a minority of patients (9.7%) underwent daily follow-up blood cultures, with no significant difference between survivors and non-survivors (11.9% vs. 8.1%; OR 0.65, 95% CI 0.30–1.41). Follow-up blood cultures available for 237 of 298 patients (79.5%), obtained either at predefined time points (e.g., days 1, 3, and 5) or at irregular intervals.

Completion of a 14-day antifungal treatment after the first documented negative blood culture was observed in 107 of 126 survivors (84.9%) and 159 of 172 non-survivors (92.4%) (p = 0.04). Guideline adherence in candidemia patients is shown in Table 4.

Table 4. Guideline adherence and EQUAL *Candida* score components in candidemia patients surviving ≥7 days (n=298)

EQUAL *Candida* Score Components	Survivor (n=126)	Non-survivor (n=172)	p	OR (95% CI)
Initial blood culture (≥40 cc)	92 (73)	104 (60.5)	**0.02**	0.56 (0.34-0.93)
Species identification, n (%)	114 (90.5)	167 (97.1)	**0.02**	3.51 (1.20-10.25)
Susceptibility testing, n (%)	110 (87.3)	157 (91.3)	0.26	1.52 (0.72-3.20)
Echocardiography, n (%)	74 (58.7)	101 (58.7)	0.99	1 (0.62-1.59)
Ophthalmoscopy, n (%)	57 (45.2)	81 (47.1)	0.81	1.07 (0.67-1.70)
Echinocandin treatment, n (%)	83 (65.9)	105 (61.5)	0.39	0.81(0.50-1.31)
De-escalation, n (%)	36 (28.6)	36 (20.9)	0.13	0.66 (0.38-1.12)

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Treatment for 14 days, n (%)	107 (84.9)	159 (92.4)	**0.04**	2.17 (1.02-4.58)
*CVC removal ≤24 hours, (%) n=255	21 (19.4)	28 (19)	0.93	0.97 (0.51-1.83)
*CVC removal >24<72 hours, (%) n=255	46 (42.6)	43 (29.3)	**0.03**	0.55 (0.33-0.93)
Follow-up blood culture (one per day), n (%)	15 (11.9)	14 (8.1)	0.27	0.65 (0.30-1.41)
**EQUAL *Candida* score, median (IQR)	13 (11-17)	13 (10-15)	0.19	

*Reference category for CVC removal variables: no catheter removal

**EQUAL *Candida* score was analyzed as a continuous variable using univariate comparisons

Kaplan–Meier survival analysis demonstrated significant differences in 30-day survival across EQUAL *Candida* score categories among patients with candidemia (n = 365). Survival probability increased progressively with higher EQUAL *Candida* score categories, with the highest survival observed in patients with scores of 16–22. The difference in survival distributions between score categories was statistically significant (log-rank p = 0.02) (Figure 1).

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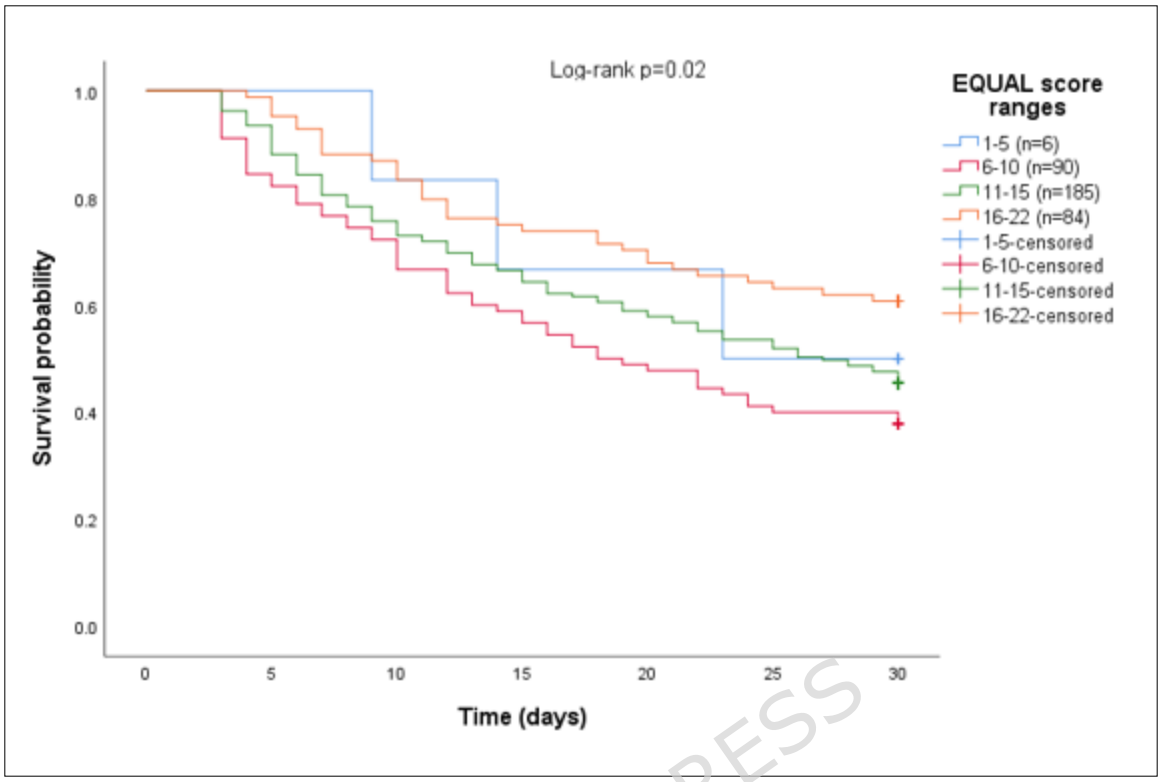


Figure 1. Kaplan–Meier survival curves showing 30-day survival according to EQUAL *Candida* score categories in candidemia patients (n = 365), excluding deaths within the first 48 hours.

Among patients with CVC-related candidemia (n = 308), Kaplan–Meier survival analysis also demonstrated significant differences in 30-day survival across EQUAL *Candida* score categories. Survival probability increased with higher EQUAL *Candida* scores, with the highest survival observed in the 16–22 score category. The difference between survival curves was statistically significant (log-rank p = 0.008) (Figure 2).

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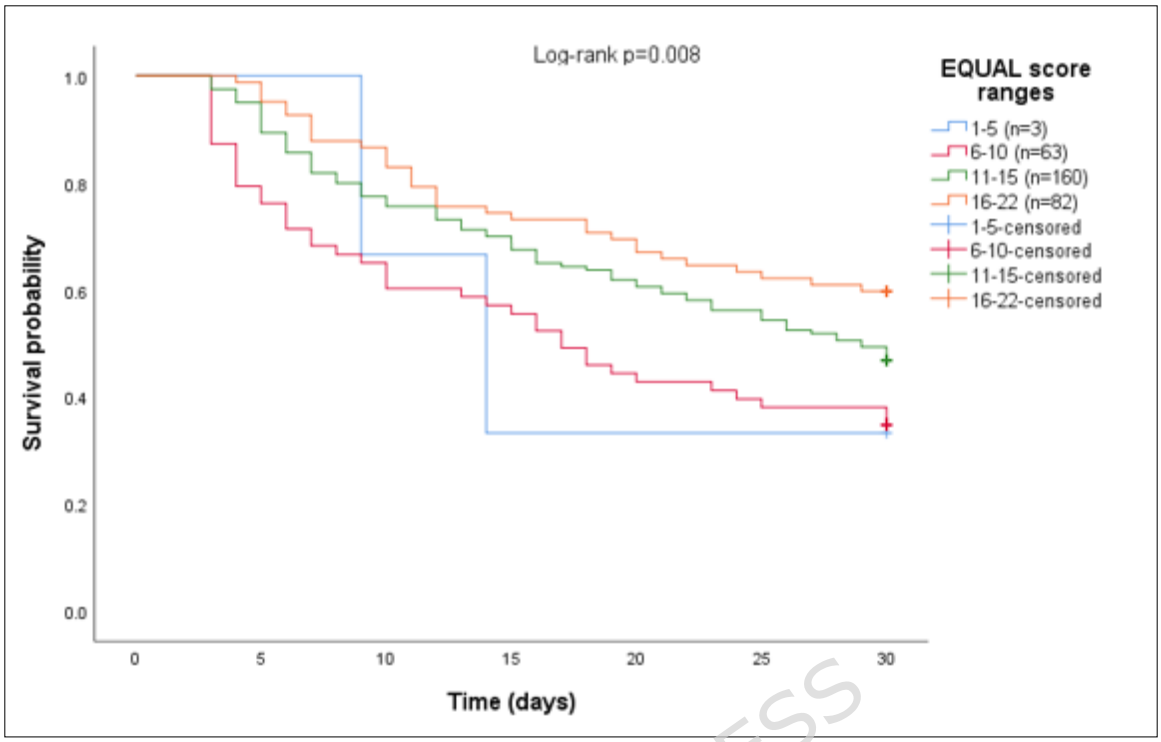


Figure 2. Kaplan–Meier survival curves showing 30-day survival according to EQUAL *Candida* score categories in patients with CVC-related candidemia (n = 308)**,** excluding deaths within the first 48 hours.

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Discussion

This nationwide multicenter study evaluated 398 candidemia episodes from 20 hospitals across different geographical regions of Turkey, providing a representative overview of candidemia in a contemporary clinical setting. The crude mortality rate was 68.3%, while 30-day mortality reached 56.3%. After exclusion of deaths occurring within the first 48 hours, 30-day mortality remained high (52.9%), indicating the substantial burden of disease in this cohort. Reported mortality rates of candidemia vary widely in the literature, ranging from below 10% in pediatric populations to over 75% among critically ill adults in ICUs, largely reflecting differences in host factors, disease severity, and healthcare settings. In a multicenter prospective study predominantly involving ICU patients in Turkey, the 30-day mortality rate was 56.7%, closely mirroring our findings [15]. Similarly, mortality rates exceeding 60% have been reported among critically ill patients with COVID-19–associated candidemia, highlighting the poor prognosis in high-risk ICU populations [16].

Advanced age and comorbidity burden were strongly associated with mortality in our cohort. Non-survivors were significantly older and had a higher prevalence of underlying diseases, and comorbidity burden remained independently associated with 30-day mortality in multivariable analysis (HR 4.45, 95% CI 1.58–

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12.52; p = 0.005). Malignancy was particularly common, affecting nearly half of the patients (44.5%). In addition, most patients were critically ill, frequently required intensive care, and commonly developed sepsis or required invasive supportive therapies. These findings indicate that candidemia outcomes in this cohort were largely influenced by host-related factors and overall disease severity, particularly among older patients with complex comorbid conditions. Similar associations between age, comorbidity burden, and mortality have been reported in previous multicenter and ICU-based candidemia studies [17-21]. Consistent with our findings, the ECMM *Candida* III study also identified disease severity as a major determinant of mortality [22].

Large multicenter European surveillance studies have demonstrated substantial geographic variation in candidemia epidemiology. In the ECMM III study, which included nearly 400 blood culture isolates from 41 centers across 17 European countries, the proportion of *C. albicans* ranged from 77% in Austria to 36% in Turkey. Compared with earlier European cohorts, this study documented a decline in *C. albicans*, accompanied by increasing proportions of *C. glabrata* and persistently high rates of *C. parapsilosis*, particularly in Southern Europe, including Italy and Turkey [22].

In line with observations reported from several regions worldwide, our findings demonstrate a predominance of NAC species in this nationwide cohort. While *C. albicans* accounted for approximately one third of isolates, NAC species (65.3%) predominated overall, reflecting a changing species landscape in contemporary clinical practice. This observation is supported by previous reports, such as the study by Yang et al., which documented a NAC proportion of 62.8% [23]. The relatively high proportion of *C. parapsilosis* in our study, accounting for approximately one quarter of isolates, is particularly noteworthy, given its well-established association with CVCs, parenteral nutrition, broad-spectrum antibiotic exposure, and prolonged hospitalization. Most patients in our study were exposed to key risk factors, with approximately 90% receiving broad-spectrum antibiotics in the preceding month and over 80% having a CVC. Disruption of the intestinal microbiota with broad-spectrum antibiotics may promote yeast overgrowth and bloodstream invasion by *C. parapsilosis*, while biofilm formation on CVCs further facilitates infection [2,24]. Regional disparities in the incidence of *C. parapsilosis*, particularly in Southern Europe, South Africa, and Latin America, have been described and may be influenced by local epidemiological patterns and infection control strategies [22,25]. In this context, studies from Turkey have reported proportions as high as 33.6% among candidemia cases, with *C. parapsilosis* being identified as the most frequent causative agent in some hospitals [15,26]. When considering that *C. parapsilosis* is often associated with catheter-related candidemia compared with other *Candida* species, this association may help explain its higher frequency in these settings. *C. glabrata* is regarded as a high-priority pathogen and has emerged as an increasingly important cause of candidemia in recent years. In many geographical regions including United States, Australia, Northern Europe, it is now reported as the second most common cause of invasive candidiasis [2,22,27]. In this study, *C. glabrata* accounted for about 15% of isolates. This finding is in line with the broader literature, including a systematic review informing the World Health Organization Fungal Priority Pathogens List, which shows

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that most studies report *C. glabrata* in about 10–30% of candidemia cases [28]. In addition, the detection of *C. auris* across multiple centers in our cohort suggests that this pathogen is no longer limited to isolated outbreaks but is becoming increasingly established in routine clinical settings, consistent with the global increase reported since 2020 [29]. Although the proportion remains relatively low, the presence of *C. auris* is clinically significant due to its propensity for healthcare-associated outbreaks and limited therapeutic options. In this context, the rising number of healthcare-associated outbreaks worldwide, including reports from Turkey, underscores *C. auris* as an emerging nosocomial pathogen [26,30]. Its rapid spread in healthcare settings, environmental persistence, biofilm formation, and multidrug resistance have led global health authorities to recognize *C. auris* as a major public health threat [29,31].

Despite the increasing diversity of *Candida* species, neither *C. albicans* nor NAC species were associated with 30-day mortality in univariate analysis, and species distribution did not remain an independent predictor of mortality in multivariate models in our patient population. Consistent with these findings, the multicenter prospective study by Kutlu et al. (2022) from Turkey reported no significant differences in mortality according to species, although *C. albicans* (39.7%) and *C. parapsilosis* (33.6%) were the most frequently isolated pathogens [15]. Similarly, Vannini et al. (2022) reported from France that crude mortality was higher among NAC infections (36%) than *C. albicans* infections (26%); however, this difference was not statistically significant ($p = 0.16$) [32]. Earlier data from Moran et al. (2009) also demonstrated comparable inpatient mortality rates in adults with *C. albicans* (41.5%) and NAC infections (44.1%) [33]. In contrast, the ECMM *Candida* III subgroup analysis reported substantial variation in attributable mortality by species, with *C. tropicalis* showing rates as high as 63.6%, while *C. albicans* and *C. parapsilosis* exhibited considerably lower attributable mortality (7.7% each) [34]. Nevertheless, these findings highlight considerable differences between studies, suggesting that the relationship between *Candida* species and mortality should be interpreted with context.

In our cohort, empirical echinocandin therapy was commonly used, in line with current guideline recommendations and routine clinical practice [35]. Empirical echinocandin therapy was not independently associated with 30-day mortality after exclusion of deaths occurring within the first 48 hours. Instead, comorbidity burden remained the only independent predictor of mortality in multivariable analysis, while commonly used markers of disease severity lost statistical significance after adjustment. These findings indicate that outcomes following the initial phase of candidemia were more closely related to underlying patient characteristics than to differences in empirical antifungal choice. In this context, timely source control—particularly removal of infected intravascular devices—appears to be an important component of management, as persistence of an infected device may allow ongoing fungal seeding despite appropriate antifungal therapy.

Central venous catheter–associated candidemia represents a severe healthcare-associated bloodstream infection with high mortality, particularly among critically ill patients. The risk of catheter-related candidemia is increased in the presence of broad-spectrum antibiotic exposure, total parenteral nutrition,

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multiple comorbidities, and prolonged ICU stay. In these settings, intravascular catheters may function both as a portal of entry and as a persistent source of bloodstream infection, and delayed source control can contribute to ongoing fungemia, sepsis, and organ dysfunction [36,37]. In our cohort, CVCs were identified as the most common source of candidemia, accounting for approximately 40% of cases. Although catheter removal was performed in more than half of patients after diagnosis, the timing of removal varied substantially. Only a minority of catheters were removed within the first 24 hours, with most removals occurring between 24 and 72 hours. Failure to remove the catheter was independently associated with increased 30-day mortality in multivariable analysis (HR 0.66, 95% CI 0.47–0.93; $p = 0.02$), and catheter removal was significantly less frequent among non-survivors than among survivors ($p < 0.001$). These findings are consistent with current international guideline recommendations that emphasize early source control, including prompt catheter removal when feasible, as a central component of candidemia management [38,39].

In univariate analysis, a history of surgery was less frequently observed among non-survivors. However, this association is unlikely to reflect a true survival benefit. Patients with prior surgery were generally younger and had fewer comorbidities than those without surgical history, factors that are well known to be associated with improved outcomes in candidemia. In addition, closer postoperative monitoring may allow earlier recognition of candidemia and more timely implementation of source control. Therefore, the observed association between prior surgery and lower mortality is more plausibly explained by residual confounding related to baseline patient characteristics and differences in clinical management, rather than a direct protective effect of surgery itself, consistent with previous observations in candidemia cohorts [40,41].

The EQUAL *Candida* score provides a practical way to apply guideline recommendations in daily clinical practice. It reflects how closely patient management follows international guidelines by combining diagnosis, antifungal treatment, source control, and follow-up into a single care bundle. Higher scores have frequently been associated with improved survival, suggesting that closer adherence to recommended practices may contribute to better outcomes. This association has been demonstrated across diverse patient populations, including a large multinational cohort of 632 candidemia cases from 20 European countries [13]. In this context, we evaluated the performance of the EQUAL *Candida* score in our study group. In the 30-day mortality analysis, EQUAL *Candida* scores were significantly lower among non-survivors ($p = 0.01$), indicating lower adherence to recommended management practices. Although the score did not remain statistically significant in the multivariable model, it showed a trend toward a lower hazard of mortality (HR 0.95, 95% CI 0.90–1.00; $p = 0.06$), suggesting that guideline-based management remains relevant in candidemia.

When the analysis was restricted to patients who survived at least seven days after candidemia onset, differences between survivors and non-survivors primarily reflected the quality of early management. Adequate diagnostic sampling and timely source control appeared to be the most influential factors, with survivors more frequently having an adequate initial blood culture volume (≥40 mL; 73% vs. 60.5%, p =

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0.02) and timely CVC removal within 24–72 hours (42.6% vs. 29.3%, p = 0.03). These findings are consistent with previous studies highlighting the critical role of early diagnostic and source control measures in candidemia management [11,37]. In contrast, species identification and completion of a full 14-day course of antifungal therapy were more commonly observed in non-survivors (p = 0.02 and p = 0.04, respectively). This pattern is most plausibly explained by survival bias, a well-recognized limitation of observational studies with time-dependent exposures, whereby patients who survive longer have a greater opportunity to complete diagnostic evaluations and prolonged courses of therapy [40,41]. No significant differences were observed for other guideline-recommended interventions, including echocardiography, ophthalmoscopy, commencing treatment with an echinocandin, de-escalation, early catheter removal (≤24 hours), or daily follow-up blood cultures.

Although median EQUAL *Candida* scores were similar between survivors and non-survivors [13 (IQR 11–17) vs. 13 (IQR 10–15), p = 0.19], Kaplan–Meier survival analysis demonstrated significant differences in 30-day survival across EQUAL *Candida* score categories. Survival increased with higher EQUAL *Candida* scores, with the highest survival observed among patients with scores of 16–22. A similar pattern was observed among patients with CVC-related candidemia, where survival also increased across higher EQUAL *Candida* score categories. While the EQUAL *Candida* score did not remain an independent predictor of mortality in the multivariable analysis, the Kaplan–Meier curves demonstrated a consistent survival gradient across score categories. This stepwise survival pattern across EQUAL *Candida* score categories has also been reported in previous studies evaluating the association between EQUAL *Candida* score and survival [42]. Taken together, these findings suggest a survival gradient across EQUAL *Candida* score categories, which may reflect better adherence to guideline-recommended candidemia management. Daily follow-up blood cultures are included in the EQUAL *Candida* score, however the evidence supporting mandatory daily sampling remains limited. Guideline recommendations are not fully consistent: while the Infectious Diseases Society of America suggests obtaining blood cultures daily or every other day until clearance, other guideline frameworks—as well as real-world clinical practice—prioritize documentation of bloodstream clearance with follow-up cultures guided by clinical response rather than strict daily sampling [38,39,43]. In our study, daily follow-up blood cultures were obtained in only a small proportion of patients (9.7%) and did not differ between survivors and non-survivors. In contrast, the majority of patients (79.5%) underwent follow-up cultures at predefined or irregular time points, reflecting routine real-world practice rather than strict daily monitoring.

This study has several limitations. First, its retrospective design may have introduced information and selection bias. Inclusion was limited to approximately 20 candidemia episodes per center, which may have reduced the ability to fully capture center-specific burden and epidemiological variability. In addition, restricting inclusion to the first candidemia case during outbreak periods may have limited the detection of temporal trends. Catheter-associated candidemia was defined using clinical and epidemiological criteria rather than strict microbiological confirmation, reflecting real-world clinical practice. Antifungal

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susceptibility testing was not standardized across centers, which limits the comparability of resistance data and precludes reliable evaluation of associations between antifungal resistance and clinical outcomes. Survival bias may have influenced certain clinical associations and EQUAL *Candida* score components, and exclusion of patients who died within the first 48 hours may have led to underestimation of the impact of severe disease. Finally, the absence of a pre-pandemic comparator cohort limits direct comparison with earlier periods. Despite these limitations, the multicenter design and large sample size enhance the generalizability of our findings and provide nationally representative real-world data.

Conclusion

Candidemia was associated with high mortality, particularly among older adults and critically ill patients with multiple comorbidities. Non-albicans *Candida* species constituted the majority of isolates in this nationwide multicenter cohort, with *C. parapsilosis* identified as the most frequent pathogen overall. The multicenter detection of *C. auris* underscores its growing clinical relevance in Turkey. Although species distribution was not independently associated with mortality in this cohort, the diagnostic complexity, limited antifungal treatment options, and potential for healthcare-associated transmission of *C. auris* highlight the need for strengthened surveillance and infection prevention strategies. Central venous catheters were identified as the predominant source of infection, and failure to remove the catheter was independently associated with increased mortality, highlighting early source control as a key modifiable factor in routine clinical practice. The EQUAL *Candida* score was useful for describing differences in survival across levels of guideline adherence in this cohort; however, host-related factors—especially comorbidity burden—remained the principal determinants of outcome. Collectively, these findings provide a contemporary nationwide overview of candidemia epidemiology in Turkey, highlighting the predominance of NAC species, the multicenter detection of *C. auris*, and the importance of early source control in clinical practice.

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Author contributions

Conceptualization, Z.C.K.; methodology, Z.C.K. and F.C.; data curation, Z.C.K.; formal analysis, Z.C.K. and Z.Y.; investigation, Z.C.K. and participating investigators; laboratory analysis, F.C., M.U., and the microbiology team; writing—original draft preparation, Z.C.K.; writing—review and editing, all authors; supervision, O.E., N.S., F.C., and R.T.; project administration, Z.C.K. All participating investigators contributed to patient recruitment, clinical data collection, and local data validation. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request, in accordance with institutional policies and ethical regulations.

Additional information

This study was conducted in accordance with the Declaration of Helsinki and approved by the Istinye University Human Research Ethics Committee (protocol code 2023/11, approval number 23-282). Patient consent was waived due to the retrospective design of the study and the use of anonymized clinical data and *Candida* isolates, in accordance with institutional and national ethical regulations. This research received no external funding.

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Competing interests

The authors declare no competing interests.

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