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Rare Conditions of Candidemia: Risk Factors and Outcomes for Mixed Candidemia and Late Recurrent Candidemia

Nadir Kandidemi Durumları: Mikst Kandidemi ve Geç Tekrarlayan Kandidemi için Risk Faktörleri ve Sonuçları

Bahadır Orkun ÖZBAY[1], Aliye BAŞTUĞ[2], Ömer AYDOS[3], Nizamettin KEMİRTLEK[3], Derya GÖKÇINAR[4], Bedia DİNÇ[5], Hürrem BODUR[2]

[1]Tokat State Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Tokat, Turkey
[2]University of Health Sciences Turkey, Gülhane Faculty of Medicine, Ankara City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
[3]Ankara City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
[4]Ankara City Hospital, Clinic of Critical Care Medicine, Ankara, Turkey
[5]Ankara City Hospital, Clinic of Medical Microbiology, Ankara, Turkey

Abstract

Introduction: Mixed candidemia (MC) and late recurrent candidemia (LRC) are rare conditions. Studies on these issues are limited. Our aim was to investigate the characteristics, risk factors, and outcomes of these rare conditions.
Materials and Methods: The study was carried out between May 2019-May 2021 in Ankara City Hospital as a cross-sectional descriptive study. Mixed candidemia was defined as the isolation of at least two Candida species in two blood culture bottles taken within 72 hours or one blood culture bottle taken simultaneously (from a patient with clinical symptoms). Late recurrent candidemia was defined as the recurrence of candidemia at least 30 days after the treatment of the first candidemia episode was completed and the symptoms resolved. In the study, MC patients were compared with monomicrobial candidemia patients. The LRC group was compared with the single episode candidemia group.
Results: During the study period, 549 candidemia episodes were detected in 533 patients. Mixed candidemia was detected in 38 (7.1%) of these patients. Late recurrent candidemia was seen in 16 (10.7%) of 149 patients who recovered after treatment and survived above 30 days. History of abdominal surgery and instrumentation, chemotherapy and transplantation were significantly higher in the MC group compared to the monomicrobial candidemia group. Compared to the single episode candidemia, the LRC group had significantly higher rate of abdominal surgery and instrumentation history, concomitant bacteremia, *Candida* colonization index of >0.5 and 1-year follow-up mortality.
Conclusion: Both MC and LRC were significantly more common in patients who had undergone abdominal surgery and instrumentation. With the development of diagnostic methods, we may encounter these rare cases more often. Since candidemia has a high mortality rate, recurrent candidemia may be overlooked. According to the results of the study, there is a 10% risk of recurrence in recovered candidemia cases.
Keywords: Candidemia, mixed candidemia, late recurrent candidemia, risk factors, mortality

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Address for Correspondence/Yazışma Adresi: Bahadır Orkun ÖZBAY MD, Tokat State Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Tokat, Turkey
Phone: +90 356 214 54 00, +90 537 867 01 57 **E-mail:** orkun-ozbay@hotmail.com **ORCID ID:** orcid.org/ 0000-0003-1681-5821
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Öz

Giriş: Mikst kandidemi ve geç tekrarlayan kandidemi nadir görülen durumlardır. Bu konulardaki çalışmalar sınırlıdır. Amacımız bu nadir durumların özelliklerini, risk faktörlerini ve sonuçlarını araştırmaktır.
Gereç ve Yöntem: Araştırma, Mayıs 2019-Mayıs 2021 tarihleri arasında Ankara Şehir Hastanesi'nde kesitsel tanımlayıcı bir çalışma olarak gerçekleştirildi. Mikst kandidemi, 72 saat içinde alınan iki kan kültürü şişesinde veya eş zamanlı alınan bir kan kültürü şişesinde (klinik semptomları olan bir hastadan) en az iki *Candida* türünün izolasyonu olarak tanımlandı. Geç tekrarlayan kandidemi, ilk kandidemi atağının tedavisi tamamlandıktan ve semptomların düzelmesinden en az 30 gün sonra kandideminin tekrarlaması olarak tanımlandı. Çalışmada mikst kandidemi hastaları ile monomikrobiyal kandidemi hastaları karşılaştırıldı. Geç tekrarlayan kandidemi grubu, tek ataklı kandidemi grubuyla karşılaştırıldı.
Bulgular: Çalışma süresi boyunca 533 hastada 549 kandidemi atağı tespit edildi. Bu hastaların 38'inde (%7,1) mikst kandidemi saptandı. Tedavi sonrası iyileşen ve 30 günden uzun yaşayan 149 hastanın 16'sında (%10,7) geç tekrarlayan kandidemi görüldü. Mikst kandidemi grubunda, monomikrobiyal kandidemi grubuna kıyasla abdominal cerrahi ve enstrümantasyon, kemoterapi ve transplantasyon öyküsü anlamlı derecede yüksekti. Geç tekrarlayan kandidemi grubu, tek ataklı kandidemi ile karşılaştırıldığında, abdominal cerrahi ve enstrümantasyon öyküsü, eşlik eden bakteriyemi, kandida kolonizasyon indeksinin >0,5 olması ve 1 yıllık takipteki mortalite anlamlı olarak daha yüksek oranda saptandı.
Sonuç: Hem mikst kandidemi hem de geç tekrarlayan kandidemide, abdominal cerrahi ve enstrümantasyon uygulanan hastalarda anlamlı derecede daha yaygın saptandı Tanı yöntemlerinin gelişmesiyle birlikte bu nadir vakalarla daha sık karşılaşabiliriz. Kandidemi yüksek mortalite oranına sahip olduğundan tekrarlayan kandidemiler gözden kaçabilir. Araştırma sonuçlarına göre iyileşen kandidemi vakalarında tekrarlama riski %10'dur.
Anahtar Kelimeler: Kandidemi, mikst kandidemi, geç tekrarlayan kandidemi, risk faktörleri, mortalite

Introduction

Candida bloodstream infections (BSIs) are an increasingly important healthcare-associated infection. In addition to being a cause of serious morbidity and mortality, *Candida* BSIs also cause increased length of hospitalization and higher costs[1,2]. Numerous studies have identified risk factors for candidemia[3-5]. However, mixed candidemia (MC) and late recurrent candidemia (LRC) are rare conditions[6,7]. Therefore, there are limited data on the characteristics, risk factors, and outcomes of the patients with MC and LRC. In this study, we aimed to answer these questions and fill this gap since early diagnosis and treatment are crucial in these infections, which have crucially higher mortality rates.

Materials and Methods

Study Design, Settings and Participants

The study was carried out between May 2019 and May 2021 in Ankara City Hospital (3,810 bed capacity including 690 intensive care unit beds) as a cross-sectional descriptive study. Ethics committee approval was obtained from Ankara City Hospital Ethics Committee (no: E1-21-1911, date: 23.06.2021). Patients over 18 years of age with *Candida* isolated in clinically significant blood cultures were included in the study. The MC patients were compared with monomicrobial candidemia. The LRC group was compared with the single episode candidemia (Figure 1). For LRC, data from the first episode were used in the study. Patients with recurrent candidemia within 30 days of recurrence were not included in the LRC group. According to the case definitions, they were included in one of the other two groups. Demographic characteristics, risk factors, type of *Candida* spp. and its susceptibility pattern, and outcomes of the patients were collected from the hospital electronic record system.

Definitions

Candidemia was defined as the isolation of one or more *Candida* isolates in at least one blood culture bottle with findings consistent with infection. MC was defined as the isolation of at least two *Candida* species in two blood culture bottles taken within 72 hours or one blood culture bottle taken simultaneously (from a patient with clinical symptoms). Late recurrent candidemia was defined as the recurrence of candidemia (any of the *Candida* species) at least 30 days after the treatment of the candidemia episode was completed and the symptoms resolved. The single episode candidemia group included patients who recovered from candidemia, lived at least 30 days, and did not have a recurrence of candidemia.

Nosocomial candidemia was defined as the patient who had candidemia at least two days after hospitalization without recent hospitalization history. In order for candidemia to be accepted as central venous catheter (CVC) related, the same *Candida* species should be isolated in the simultaneous catheter culture with the peripheral blood culture. Previous use of broad-spectrum antibiotics was defined as the use of one or more antipseudomonal cephalosporins, piperacillin-tazobactam, carbapenems, fosfomycin, colistin, and tigecycline antibiotics within one month. High-dose steroid was defined as using more than 15 mg of prednisolone (or its' equivalent) for more than three weeks. Receiving chemotherapy within the last month was classified as a possible risk factor. Neutropenia was defined as the presence of absolute neutrophil count less than $0.5x10^9$/L. Abdominal intervention history was defined as having abdominal surgery or gastric instrumentation within three months. In the study, in order for total parenteral nutrition

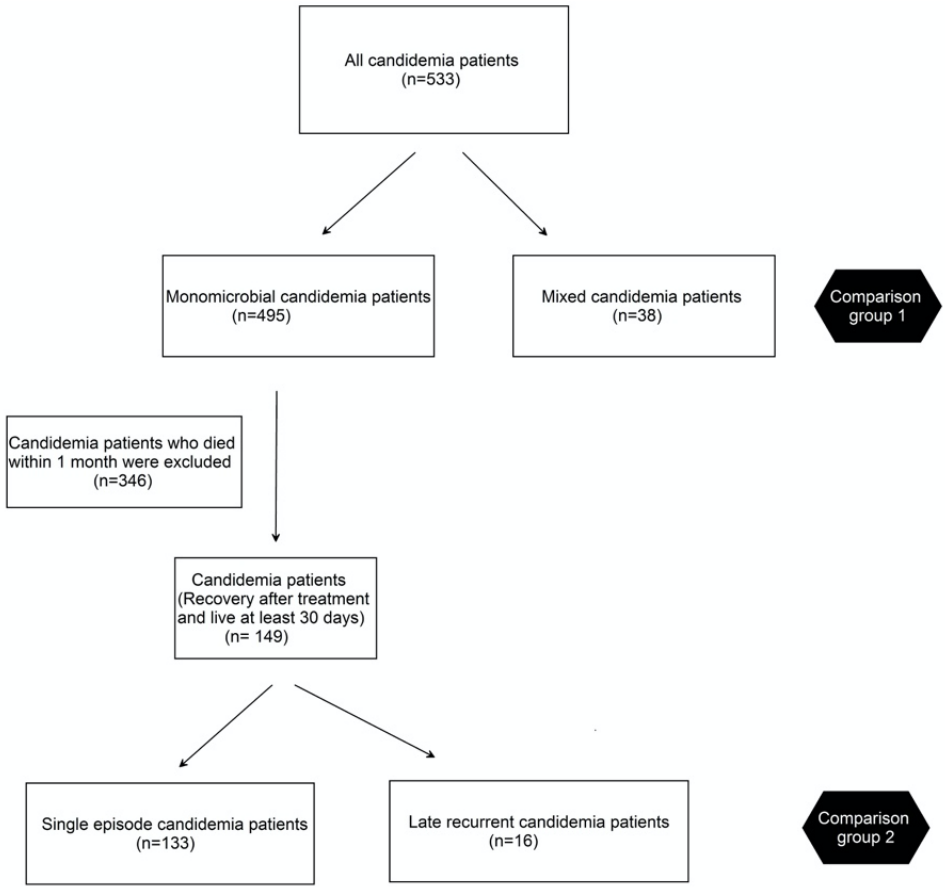

Figure 1. Flow chart

(TPN), mechanical ventilation and central venous catheter use to be considered as possible risk factors, it should have started at least two days before candida isolation. *Candida* colonization index (CCI) (CCI=Number of sites colonized/number of sites cultured, threshold >0.5)[8] and *Candida* score [multifocal colonization (1 point), sepsis (2 points), surgery (1 point), TPN (1 point), threshold >2.5][9] were also evaluated among the possible risk factors in the study.

Early mortality was defined as deaths occurring within seven days of *Candida* isolation. Related mortality was defined as death occurring within five days of candidemia without any other concurrent signs of infection and no other apparent cause[6]. In the one-year follow-up of mortality in LRC patients, the one-year period after the second attack of candidemia was considered. One-year mortality follow-up was followed from hospital electronic records and national death notification system. The taxonomy of the species previously included in the genus *Candida* has changed. Since this update would not make a difference to clinical practice, the old taxonomy was followed.

Microbiological Identification

Microbiological tests of the study were performed in Ankara City Hospital central microbiology laboratory. The BacT/Alert (bioMérieux) automated blood culture system was used for monitoring blood culture bottles. *Candida* spp. isolates were identified using the VitekMS (bioMérieux) device and the MALDI-TOF MS method. Susceptibility tests were evaluated with the VITEK® 2 Compact automated system (bioMérieux, France) according to the European Committee on Antimicrobial Susceptibility Testing.

Statistical Analysis

For those without normal distribution in descriptive statistics on continuous variables were calculated as median, interquartile range (IQR) [Quartile 1 - Quartile 3 (Q1 - Q3)]. For categorical variables, count and percentages were calculated. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov test). The Pearson chi-square test and the Fisher's exact probability test were used to compare categorical variables. Student's t-test and the Mann-Whitney U test were used for continuous variables. Statistical significance level was accepted as $p<0.05$. IBM Statistical Package for the Social Sciences statistics for Windows (IBM Corp. Released 2013. version 22.0. Armonk, NY: IBM Corp.) program was used for statistical analyses.

Results

During the study period, 549 candidemia episodes were detected in 533 patients. Mixed candidemia was observed in 38 (7.1%) patients. Late recurrent candidemia was seen in 16 (10.7%) of 149 patients who recovered after treatment and lived longer than 30 days. In 549 candidemia episodes, 587 *Candida* spp. were isolated, such as *C. albicans* (n=278, 47.4%), *C. parapsilosis* (n=124, 21.1%), *C. glabrata* (n=79, 13.4%), and *C. tropicalis* (n=68, 11.6%), in order of frequency. In addition, a total of 10 different *Candida* species were isolated from the patients in the study (Table 1). When all groups were examined separately, it was determined that *C. albicans* was the most frequently isolated one. Isolated *Candida* species in MC and LRC were detailed in Tables 2 and 3.

Mixed Candidemia

Of 38 MC patients, 15 were male and the median age of the patients was 68 years (IQR: 56-79). The most common comorbidity in MC patients was hypertension (39.5%), and the most common risk factors for candidemia in these patients were CVC (100%), previous use of broad-spectrum antibiotics (97.4%), and mechanical ventilation (89.5%), respectively. Concomitant bacteremia was detected in 15 (39.5%) patients. Characteristics, treatments, and outcomes of MC patients are shown in Table 2. During the follow up, 33 (86.8%) of the MC patients died. It was recorded as a candidemia-related death in 12 (31.5%) patients.

In the comparison of MC patients with monomicrobial candidemia patients, MC was found to be significantly higher in female patients [p=0.044; odds ratio (OR)=1.981, 95% confidence interval (CI)=1.009-3.887], and those with a history of abdominal surgery and instrumentation (p=0.018; OR=2.276, 95% CI=1.136-4.557), chemotherapy (p=0.042; OR=2.338, 95% CI=1.054-5.185), and transplantation (p=0.047; OR=4.629, 95% CI=1.199-17.871). In addition, ocular involvement (p=0.04; OR=9.219, 95% CI=1.57-54.142) was significantly higher in the MC group compared to the control group. Detailed comparison of MC and monomicrobial candidemia is shown in Table 4.

Table 1. Species distribution of candidemia isolates

Candida species	n (%)
C. albicans	278 (47.4)
C. parapsilosis	124 (21.1)
C. glabrata	79 (13.4)
C. tropicalis	68 (11.6)
C. kefyr	12 (2)
C. krusei	10 (1.7)
C. lusitaniae	8 (1.4)
C. dubliniensis	5 (0.9)
C. guilliermondii	2 (0.3)
C. inconspicua	1 (0.2)
Total	587 (100)

Table 2. Characteristics, treatments and outcome of patients with mixed candidemia

Patient no	Gender/ age	Comorbidities	Risk factors	*Candida* spp.	Antifungal treatment	Positive cultures other than blood culture	Concomitant bacteriemia (±3 days)	Outcome
1	F/88	Vulvar cancer	CVC, GS, BSA, HdC, CT	*C. albicans* *C. kefyr*	Echinocandin			Died
2	M/79	DM, HT	CVC, BSA, COV, HdC	*C. albicans* *C. tropicalis*	Fluconazole			Died
3	M/59	DM	CVC, TPN, GS, BSA	*C. glabrata* *C. parapsilosis*	Echinocandin	Urine		Died
4	M/80	DM, HT	CVC, BSA	*C. albicans* *C. parapsilosis*	Echinocandin			Died
5	F/70	Pancreatic cancer	CVC, GS, BSA, CT	*C. albicans* *C. glabrata*	Echinocandin	Urine		Died
6	M/66	HT, CHF	CVC, BSA, HdC, COV	*C. tropicalis* *C. krusei*	Echinocandin	Urine, DTA	*E. faecium*	Died
7	F/38	DM, CKD	CVC, BSA	*C. albicans* *C. parapsilosis*	Echinocandin	Urine, DTA		Died

Table 2. Continued

Patient no	Gender/ age	Comorbidities	Risk factors	*Candida* spp.	Antifungal treatment	Positive cultures other than blood culture	Concomitant bacteriemia (±3 days)	Outcome
8	F/69	DM, HT	CVC, HdC, BSA, N	*C. parapsilosis* *C. lusitaniae*	Echinocandin	Urine, DTA		Died
9	M/56	Soft tissue cancer	CVC, CT	*C. glabrata* *C. parapsilosis*	Echinocandin		*S. aureus*	Died
10	M/62	CHF	CVC, TPN, HdC, BSA	*C. albicans* *C. parapsilosis*	Echinocandin		*Stenotrophomonas maltophilia*	Died
11	M/54	COPD, CHF, lung transplantation	CVC, TPN, HdC, BSA	*C. albicans* *C. glabrata*	Voriconazole		*E. coli*	Died
12	F/73	DM, CHF	CVC, COV, BSA, HdC	*C. glabrata* *C. parapsilosis*	Echinocandin	Urine, DTA	*K. pneumoniae*	Died
13	F/77	DM, HT	CVC, BSA, HdC	*C. albicans* *C. glabrata*	Fluconazole	Urine		Died
14	F/46	Thyroid cancer	CVC, CT, TPN, BSA, COV	*C. albicans* *C. glabrata*	Echinocandin			Cured
15	F/80	HT	CVC, COV, BSA, HdC	*C. parapsilosis* *C. tropicalis*	Echinocandin	Urine		Died
16	M/46	None	CVC, COV, BSA, HdC	*C. albicans* *C. kefyr*	Fluconazole	Urine		Died
17	M/91	CKD, CHF	CVC, TPN, BSA	*C. albicans* *C. tropicalis*	Fluconazole			Died
18	F/62	CKD, CHF	CVC, TPN, HdC, BSA	*C. albicans* *C. glabrata*	Echinocandin	Urine	*K. pneumoniae*	Died
19	M/73	CHF, CVD	CVC, TPN, BSA, HdC	*C. albicans* *C. tropicalis*	Echinocandin			Died
20	M/79	DM, HT, CHF, CVD	CVC, BSA, GS	*C. albicans* *C. glabrata*	Echinocandin			Died
21	F/44	HT	CVC, COV, TPN, HdC, BSA	*C. glabrata* *C. tropicalis*	Echinocandin	Urine	*A. baumannii*	Cured
22	F/29	Gastric cancer	CVC, CT, BSA, GS	*C. albicans* *C. glabrata*	Echinocandin			Died
23	F/79	DM, HT, CHF	CVC, TPN, GS, BSA	*C. parapsilosis* *C. tropicalis*	Echinocandin	Urine	*E. faecalis*	Died
24	F/82	CHF, colon cancer	CVC, TPN, GS, BSA, CT	*C. albicans* *C. tropicalis*	Echinocandin		*A. baumannii*	Died

Table 2. Continued

Patient no	Gender/ age	Comorbidities	Risk factors	*Candida* spp.	Antifungal treatment	Positive cultures other than blood culture	Concomitant bacteriemia (±3 days)	Outcome
25	F/67	DM, HT, endometrial cancer	CVC, TPN, GS, BSA	*C. glabrata* *C. parapsilosis*	Echinocandin		*K. pneumoniae*	Died
26	F/79	HT, COPD, ovarian cancer	CVC, TPN, BSA, GS, HdC	*C. glabrata* *C. tropicalis*	Echinocandin	Urine, DTA		Died
27	F/90	HT	CVC, TPN, BSA	*C. glabrata* *C. tropicalis*	Echinocandin		*S. aureus*	Died
28	F/62	DM, ovarian cancer	CVC, TPN, CT, GS, BSA	*C. albicans* *C. glabrata*	Echinocandin			Died
29	F/44	Nasopharyngeal cancer	CVC, CT, BSA	*C. albicans* *C. tropicalis*	Echinocandin	DTA	*A. baumannii*	Died
30	F/70	DM, HT, CHF, CVD	CVC, TPN, BSA, GS	*C. albicans* *C. tropicalis*	Echinocandin	Urine		Died
31	M/63	DM, HT, CKD	CVC, TPN, BSA	*C. glabrata* *C. parapsilosis*	Echinocandin	DTA		Died
32	F/47	Cirrhosis, liver transplantation	CVC, TPN, GS, BSA, HdC	*C. albicans* *C. tropicalis*	Echinocandin	Urine	*K. pneumoniae*	Died
33	F/85	DM, HT	CVC, TPN, BSA	*C. albicans* *C. parapsilosis*	Echinocandin	Urine		Cured
34	M/58	Esophageal cancer	CVC, TPN, GS, BSA, CT	*C. glabrata* *C. parapsilosis*	Echinocandin		*E. faecium*	Cured
35	F/81	COPD, CHF	CVC, BSA, TPN, HdC	*C. glabrata* *C. parapsilosis*	Echinocandin	Urine		Died
36	M/19	CHF, heart transplantation	CVC, TPN, BSA	*C. glabrata* *C. parapsilosis*	Echinocandin		*K. pneumoniae*	Cured
37	M/56	COPD, CKD	CVC, TPN, BSA, HdC	*C. albicans* *C. parapsilosis*	Echinocandin	DTA		Died
38	F/88	Gastric cancer	CVC, GS, BSA	*C. glabrata* *C. kefyr*	Echinocandin			Died

M: Male, F: Female, DM: Diabetes mellitus, HT: Hypertension, CHF: Congestive heart failure, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, CVC: Central venous catheter, GS: Gastrointestinal surgery and instrumantation, BSA: Broad spectrum antibiotics, HdC: High-dose corticosteroid, TPN: Total parenteral nutrition, CT: Chemotherapy, COV: Coronavirus disease-2019, N: Neutropenia, DTA: Deep tracheal aspirate

Table 3. Characteristics, treatments and outcome of patients with late recurrent candidemia

				Initial episode					
Patient no	**Gender/ age**	**Comorbidities**	**Risk factors**	**First episode *Candida* spp.**	**Fluconazole resistance**	**Treatment**	**Source**	**Nosocomial/ community**	**Discharged**
1	M/67	HT	CVC, TPN, BSA, COV, HdC, GS	*C. albicans*	S	Echinocandin	Abdominal	Nosocomial	No
2	F/88	DM, HT, CHF	CVC, BSA	*C. albicans*	S	Echinocandin	Unknown	Nosocomial	No
3	F/53	KLL, HSCT	CVC, BSA, CT	*C. albicans*	R	Echinocandin	Catheter	Nosocomial	No
4	F/61	None	COV, CVC, TPN, BSA, GS	*C. albicans*	S	Echinocandin	Unknown	Community	No
5	M/62	COPD, lung transplantation	CVC, TPN, BSA	*C. dupliensis*	S	Echinocandin	Catheter	Nosocomial	No
6	M/66	DM, HT, CHF	CVC, BSA, GS	*C. tropicalis*	ND	Voriconazole	Abdominal	Nosocomial	No
7	M/57	DM, COPD, CHF	CVC, TPN, HdC	*C. albicans*	S	Echinocandin	Catheter	Nosocomial	No
8	F/49	CHF	CVC, TPN, BSA	*C. albicans*	S	Echinocandin	Catheter	Nosocomial	No
9	F/84	DM, HT, CHF, CVD	CVC, BSA	*C. parapsilosis*	S	Echinocandin	Catheter	Nosocomial	No
10	F/86	CVD, CHF	CVC, TPN, BSA	*C. tropicalis*	S	Echinocandin	Catheter	Nosocomial	No
11	M/60	CHF, CVD	CVC, TPN, BSA, GS	*C. tropicalis*	S	Echinocandin	Abdominal	Nosocomial	Yes
12	F/73	DM, HT, CHF, CVD	CVC, BSA,	*C. albicans*	S	Echinocandin	Catheter	Nosocomial	No
13	M/75	HT, CVD	CVC, TPN, BSA, GS	*C. albicans*	S	Echinocandin	Abdominal	Nosocomial	Yes
14	F/61	Pancreatic cancer	CVC, TPN, BSA, GS, CT	*C. albicans*	S	Echinocandin	Abdominal	Nosocomial	No
15	M/56	Esophageal cancer	CVC, TPN, BSA, GS, CT	*C. albicans*	S	Fluconazole	Abdominal	Nosocomial	No
16	F/58	DM, HT	CVC, TPN, BSA, GS, HdC	*C. parapsilosis*	R	Echinocandin	Catheter	Nosocomial	No

Late Recurrent Candidemia

The median time between patients' candidemia episodes was 70 (IQR: 40-138) days. Seven of the 16 LRC patients were male and the median age of the patients was 61.5 (IQR: 57-75). Hypertension (n=7, 43.8%) was the most common comorbidity in LRC patients. In addition, the most common risk factors in patients were CVC (n=16, 100%) and previous use of broad-spectrum antibiotics (n=15, 93.8%), in order of frequency. The *Candida* species isolated in the patients, antifungal resistance status of the isolates, treatments, and outcomes are summarized in Table 3.

Compared to the single episode candidemia group, the LRC group had a significantly higher rate of abdominal surgery and instrumentation history (p=0.042; OR=3.03, 95% CI=1.054-8.712), concomitant bacteremia (p=0.024; OR=3.214, 95% CI=1.117-9.249), CCI of >0.5 (p=0.011; OR=4.936, 95% CI=1.078-22.596), and 1-year follow-up mortality (p<0.001; OR=6.5, 95% CI=1.979-21.349). The detailed comparison of the LRC and single episode candidemia groups for risk factors and outcomes is presented in Table 5.

Discussion

In our study, the proportion of MC was 7.1%. Different rates (1.9-5.3%) of MC have been reported in the literature[10,11]. One reason for this is differences in the definition of MC in the studies. In some studies, isolation of different *Candida* spp. in a single culture is accepted, while in others, isolating different *Candida* within three days is accepted as MC[10,11]. Another reason for the variation in incidence values between studies may be the difference in the microbiological methodology. In our study, the MALDI-TOF MS method was used for *Candida* identification. The use of MALDI-TOF has a high accuracy in the identification of clinical pathological yeasts[12]. This can be considered as one of the strengths of our study. Increasing detection of MC with developing methods and the detection of resistant strains may lead to appropriate treatments. Mixed candidemia has been associated with high mortality in the literature[10,11] More studies are needed as it is a rare condition.

Overall, in our study *C. albicans* has been the most frequently isolated *Candida* species, and *C. parapsilosis* has been the

Table 3. Continued

		Recurrent episodes					
Patient no	**Time between episodes of candidemia**	**Recurrent episode *Candida* spp.**	**Fluconazole resistance**	**Treatment**	**Source**	**Nosocomial/ community**	**Outcome (cured/died)**
1	60	*C. parapsilosis*	S	Echinocandin	Abdominal	Nosocomial	Died
2	35	*C. parapsilosis*	R	Echinocandin	Catheter	Nosocomial	Died
3	141	*C. parapsilosis*	R	Echinocandin	Catheter	Nosocomial	Died
4	62	*C. parapsilosis*	R	Echinocandin	Catheter	Nosocomial	Died
5	46	*C. albicans*	S	Echinocandin	Catheter	Nosocomial	Died
6	105	*C. tropicalis*	ND	Voriconazole	Abdominal	Nosocomial	Died
7	39	*C. parapsilosis*	R	Echinocandin	Catheter	Nosocomial	Died
8	186	*C. albicans*	S	Echinocandin	Catheter	Nosocomial	Died
9	33	*C. parapsilosis*	S	Echinocandin	Catheter	Nosocomial	Cured
10	53	*C. parapsilosis*	S	Echinocandin	Catheter	Nosocomial	Died
11	166	*C. tropicalis*	S	Echinocandin	Abdominal	Nosocomial	Cured
12	35	*C. glabrata*	R	Amphotericin B	Catheter	Nosocomial	Died
13	127	*C. parapsilosis*	R	Echinocandin	Abdominal	Nosocomial	Cured
14	520	*C. tropicalis*	S	Echinocandin	Abdominal	Nosocomial	Died
15	78	*C. parapsilosis*	S	Echinocandin	Abdominal	Nosocomial	Cured
16	107	*C. parapsilosis*	R	Echinocandin	Catheter	Nosocomial	Died

M: Male, F: Female, DM: Diabetes mellitus, HT: Hypertension, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, HSCT: Haematopoietic stem cell transplantation, CVC: Central venous catheter, GS: Gastrointestinal surgery and instrumantation, BSA: Broad spectrum antibiotics, HdC: High-dose corticosteroid, TPN: Total parenteral nutrition, CT: Chemotherapy, COV: Coronavirus disease-2019, S: Susceptible, R: Resistant, ND: No data

Table 4. Comparison of features, risk factors and outcomes of mixed candidemia and monomicrobial candidemia

Category	**Variable**	**Mixed candidemia (n=38)**	**Monomicrobial candidemia (n=495)**	**Odds ratio (95% CI)**	**p value**
Demographics	Age, median (IQR[†])	68 (56-79)	72 (62-83)		0.129
	Gender, female	23 (60.5)	216 (43.6)	1.981 (1.009-3.887)	**0.044**
Comorbidities	Hypertension	15 (39.5)	262 (52.9)	0.580 (0.296-1.138)	0.110
	Diabetes mellitus	14 (36.8)	165 (33.3)	1.167 (0.588-2.315)	0.659
	Heart failure	14 (36.8)	155 (31.4)	1.276 (0.642-2.533)	0.486
	Solid tumor (in the last 1 year)	12 (31.6)	103 (20.8)	1.757 (0.857-3.6)	0.120
	Malignancy (in the last 1 year)	12 (31.5)	114 (23)	1.543 (0.754-3.154)	0.232
	Chronic kidney disease (end stage)	5 (13.2)	54 (10.9)	1.237 (0.463-3.304)	0.597
	Chronic obstructive pulmonary disease	4 (10.5)	83 (16.8)	0.584 (0.202-1.690)	0.316
	Cerebrovascular disease	3 (7.9)	71 (14.3)	0.512 (0.153-1.709)	0.268
	Liver cirrhosis	1 (2.6)	8 (1.6)	1.645 (0.200-13.510)	0.489
	Hematological malignancy (in the last 1 year)	0 (0)	11 (2.2)		1.00

Table 4. Continued

Category	Variable	Mixed candidemia (n=38)	Monomicrobial candidemia (n=495)	Odds ratio (95% CI)	p value
Risk factors	Central venous catheter (≥2 days)	38 (100)	478 (96.6)		0.624
	Prior use of broad-spectrum antibiotics (within 1 month)	37 (97.4)	468 (94.5)	2.135 (0.282-16.153)	0.712
	Mechanical ventilation (≥2 days)	34 (89.5)	413 (83.4)	1.688 (0.583-4.885)	0.329
	Sepsis	33 (86.8)	411 (83)	1.349 (0.512-3.556)	0.544
	Total parenteral nutrition (2≥ days)	22 (57.9)	244 (49.3)	1.414 (0.725-2.758)	0.307
	Concomitant bacteraemia ±3 days	15 (39.5)	157 (31.7)	1.404 (0.713-2.764)	0.324
	Abdominal surgery and instrumantation (within 3 months)	14 (36.8)	101 (20.4)	2.276 (1.136-4.557)	**0.018**
	COVID-19 (reason for hospitalization)	7 (18.4)	155 (31.3)	0.495 (0.213-1.150)	0.096
	Burned patients	0 (0)	7 (1.5)		1.00
	Presence of *Candida* in the urine	17 (44.7)	227 (45.1)	0.956 (0.492-1.856)	0.894
	Presence of *Candida* in the DTA sample	8 (21.1)	93 (18.2)	1.153 (0.512-2.596)	0.731
	Candida colonization index (>0.5)	20 (52.6)	271 (54.7)	0.918 (0.474-1.779)	0.801
	Candida risk score (≥3 points)	29 (76.3)	312 (65.1)	1.725 (0.798-3.729)	0.162
Immunosuppression	High dose corticosteroid therapy (within 1 month)	17 (44.7)	267 (53.9)	0.691 (0.356-1.342)	0.273
	Chemotherapy (within 1 month)	9 (23.7)	58 (11.7)	2.338 (1.054-5.185)	**0.042**
	Transplantation	3 (7.9)	9 (1.8)	4.629 (1.199-17.871)	**0.047**
	Neutropenic patient (<0.5x10^9/L)	1 (2.6)	6 (1.2)	2.203 (0.258-18.782)	0.406
Complications	Ophthalmic involvement (chorioretinitis, endophthalmitis)	2 (11.1)	4 (0.8)	9.219 (1.57-54.142)	**0.04**
	Cardiac involvement (endocarditis)	2 (10.5)	9 (1.8)	4.013 (0.804-20.039)	0.123
	Intraabdominal complications (abnormal findings on abdominal CT)	0 (0)	13 (2.6)		1.00
Outcome	Mortality	33 (86.8)	400 (80.8)	1.568 (0.596-4.122)	0.359
	Early mortality (<7 days)	14 (43.8)	227 (45.9)	0.689 (0.348-1.363)	0.282
	30-day mortality	25 (80.6)	346 (69.8)	0.811 (0.401-1.616)	0.540
	Related mortality	12 (31.5)	193 (38.9)	0.606 (0.288-1.274)	0.183
	ICU stay day after candidemia, median (IQR)	11 (3-29)	8 (3-20)		0.170
	ICU stay day after candidemia, excluding those who died, median (IQR)	16 (3-104)	18 (10-33)		0.912
	Time between onset of candidemia and death, median (IQR)	11 (3-27)	6 (2-16)		0.096

*The results in the table are presented as n (%) unless stated otherwise.

†Interquartile range (25-75%), IQR: Interquartile range, ICU: Intensive care unit, CT: Computed tomography, DTA: Deep tracheal aspirate, COVID-19: Coronavirus disease-2019, CI: Confidence interval

Table 5. Comparison of features, risk factors and outcomes of late recurrent candidemia and single episode candidemia

Category	Variable†	Late recurrent candidemia* (n=16)	Single episode candidemia (n=133)	Odds ratio (95% CI)	p value
Demographics	Age, median (IQR†)	61.5 (57-75)	71 (56-81)		0.413
	Gender, female	9 (56.3)	56 (42.1)	1.768 (0.621-5.032)	0.281
Comorbidities	Heart failure	8 (50)	28 (21.1)	3.750 (1.293-10.878)	**0.025**
	Hypertension	7 (43.8)	68 (51.1)	0.743 (0.262-2.113)	0.577
	Diabetes mellitus	6 (37.5)	49 (36.8)	1.029 (0.352-3.004)	0.959
	Cerebrovascular disease	5 (31.3)	27 (20.3)	1.785 (0.572-5.571)	0.338
	Malignancy (in the last 1 year)	3 (18.8)	18 (13.5)	1.474 (0.382-5.688)	0.702
	Chronic obstructive pulmonary disease	2 (12.5)	19 (14.3)	0.857 (0.180-4.076)	1.00
	Solid tumor (in the last 1 year)	2 (12.5)	17 (12.7)	1.045 (0.217-5.026)	1.00
	Hematological malignancy (in the last 1 year)	1 (6.3)	1 (0.8)	8.800 (0.523-148.048)	0.204
	Chronic kidney disease (end stage)	0 (0)	14 (10.5)		0.365
	Liver cirrhosis	0 (0)	1 (0.8)		1.00
Risk factors	Central venous catheter (≥2 days)	16 (100)	131 (98.5)		1.00
	Prior use of broad-spectrum antibiotics (within 1 month)	15 (93.8)	125 (94)	0.960 (0.112-8.215)	1.00
	Mechanical ventilation (≥2 days)	14 (87.5)	99 (74.4)	2.404 (0.520-11.124)	0.359
	Sepsis	14 (87.5)	89 (66.9)	3.461 (0.753-15.902)	0.150
	Total parenteral nutrition (2≥ days)	11 (68.8)	68 (51.1)	2.103 (0.693-6.384)	0.285
	Concomitant bacteraemia ±3 days	9 (56.3)	38 (28.6)	3.214 (1.117-9.249)	**0.024**
	Abdominal surgery and instrumantation (within 3 months)	8 (50)	33 (24.8)	3.030 (1.054-8.712)	**0.042**
	COVID-19 (reason for hospitalization)	2 (12.5)	31 (23.3)	0.219 (0.028-1.728)	0.195
	Burned patients	0 (0)	4 (3)		1.00
	Presence of *Candida* in the urine	11 (68.8)	63 (47.4)	2.444 (0.805-7.422)	0.106
	Presence of *Candida* in the DTA sample	6 (37.5)	21 (15.8)	3.200 (1.050-9.752)	**0.044**
	Candida colonization index (>0.5)	14 (87.5)	72 (54.1)	5.931 (1.297-27.125)	**0.011**
	Candida risk score (>2.5 points)	14 (87.5)	78 (58.6)	4.936 (1.078-22.596)	**0.025**
Immunosuppression	High dose corticosteroid therapy (within 1 month)	4 (25)	68 (51.1)	0.743 (0.262-2.113)	0.577
	Chemotherapy (within 1 month)	3 (18.8)	10 (7.5)	2.838 (0.692-11.640)	0.148
	Transplantation	1 (6.3)	3 (2.3)	2.889 (0.282-29.556)	0.368
	Neutropenic patient (<$0.5x10^9$/L)	0 (0)	2 (1.5)		1.00
Complications	Ophthalmic involvement (chorioretinitis, endophthalmitis)	2 (15.4)	3 (2.2)	4.545 (0.681-30.324)	0.147
	Cardiac involvement (endocarditis)	0 (0)	5 (3.7)		1.00
	Intraabdominal complications (abnormal findings on abdominal CT)	2 (16.7)	8 (6)	1.650 (0.306-8.908)	0.625
Outcome	1-year follow-up mortality	12 (75)	42 (31.6)	6.500 (1.979-21.349)	**<0.001**

*The first episode of candidemia was included in the study. †The results in the table are presented as n (%) unless stated otherwise.

†Interquartile range (25-75%), IQR: Interquartile range, CT: Computed tomography, DTA: Deep tracheal aspirate, COVID-19: Coronavirus disease-2019, CI: Confidence interval

second common. In many other studies, *C. albicans* has been seen most frequently[10,13]. In the study, the combination of *C. glabrata* and *C. parapsilosis* was the most frequently isolated combination in patients with MC. In other studies, *C. albicans* and *C. glabrata* were the most common combination[6,10]. According to the literature, the incidence of *C. parapsilosis* in nosocomial candidemia is gradually increasing[13-15].

Compared with the monomicrobial candidemia group, the history of abdominal surgery and chemotherapy was found to be higher in the MC group. In the study of Boktour et al.[16] in cancer patients, it was found that receiving chemotherapy within one month was significant for MC, as in our study. Disruption of the integrity of the intestinal mucosa by abdominal surgery and chemotherapy may cause microbial translocation.

Late recurrent candidemia was seen in 16 (10.7%) of the 149 patients who recovered after treatment and lived longer than 30 days. In other studies, in the literature, LRC has been reported between 2-9%[7,17]. Candidemia is a clinical condition with high mortality[2]. Most of the patients die in the early period[18]. Approximately 70% of the 495 patients in the monomicrobial candidemia group died within 30 days. For this reason, there is a group of patients for whom we did not know whether candidemia will recur. This situation complicates the investigation of LRC cases. According to recovered candidemia patients, there is a risk of the recurrence of candidemia in 1 out of every 10 patients with a history of candidemia. Therefore, LRC may be an overlooked condition.

The median time between the first and second episodes was 70 (2.3 months) days. The longest recurrence period was 520 days. The longest time to recurrence in the literature was reported as 14 years[19]. In the literature, the median duration of recurrence varies between 1 and 6 months[7,17,19,20]. In our study, abdominal surgery and instrumentation were associated with LRC. In other studies, gastrointestinal diseases have been found to be associated with LRC[7,19,20]. Gastrointestinal *Candida* colonization is likely to cause hematogenous spread in the LRC patients. In our study, 1-year mortality was observed as 75% in LRC patients (p=<0.001). In previous studies, mortality rates were found to be higher (45-50%) in the LRC group compared to the control group, but it was not statistically significant[7,20]. *C. parapsilosis* was isolated in the second episode in 10 (62.5%) of the LRC patients. In seven of these patients, the source of candidemia was found to be the catheter. Munoz et al.[7] also found similar results in their studies. *C. parapsilosis* typically forms a biofilm on catheters and similar implanted devices[21].

The number of cases (549) is not relatively low for a two-year follow-up. Guerra-Romero et al.[22] reported 645 cases in 13 years of follow-up (1972-1985). Jensen et al.[6] reported 747 cases in their 21-year follow-up (1985-2006). Ramos et al.[10] reported 779 candidemia episodes in a multicenter study with the participation of 29 hospitals between 2010 and 2011. According to the literature, the frequency of candidemia is increasing[14]. In particular, nosocomial candidemia has increased in the last few decades[13,15]. In addition, its frequency may vary according to the region where candidemia is reported[23].

Study Limitations

The limitation of the study is that the follow-up period of the study was two years. Since rare cases were investigated in the study, the small number of patients and the retrospective nature of the study are the limitations of the study. Multicenter studies may be performed for these rare conditions. In addition to the current limitations, the fact that many cases may have been missed when the growth performance of *Candida* species in blood culture is considered, no matter how well the identification is performed. Another limitation of the study is that confounding control could not be made through multivariate analyses. The strengths of the study are the clear definition of LRC and the exclusion of patients who died within one month from the single episode candidemia group. This situation prevents the bias that may occur in the study. Another strength of our study is the use of MALDI-TOF for *Candida* isolation. The use of MALDI-TOF has high accuracy in the identification of clinical pathological yeasts.

Conclusion

Both MC and LRC were significantly more common in patients who had undergone abdominal surgery and instrumentation. With the development of diagnostic methods, we may encounter these rare cases more often. Since candidemia has a high mortality rate, recurrent candidemia may be overlooked. According to the results of the study, it should be taken into account that late recurrence may occur in one out of every ten surviving candidemia cases.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Ankara City Hospital Ethics Committee (no: E1-21-1911, date: 23.06.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: B.O.Ö., A.B., H.B., Concept: B.O.Ö., A.B., D.G., B.D., H.B., Design: B.O.Ö., A.B., N.K., D.G., B.D., H.B., Data Collection or Processing: B.O.Ö., A.B., Ö.A., N.K., H.B., Analysis or Interpretation: B.O.Ö., A.B., Ö.A., N.K., Literature Search: B.O.Ö., Ö.A., N.K., B.D., Writing: B.O.Ö., H.B.

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