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Fungemia due to Rare Yeasts Other Than *Candida*: 10 Years of Single-center Experience

Candida Dışında Görülen Mayalarla Gelişen Fungemiler: 10 Yıllık Tek Merkez Deneyimi

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Abstract

Introduction: Fungemia due to rare yeasts other than *Candida* (RYOC) has been increasingly reported; however, data on the management of patients are limited. This study aimed to determine antifungal susceptibility profiles of the isolates and clinical characteristics, management, and outcomes of patients with fungemia due to RYOC in a tertiary-care university hospital.

Materials and Methods: Between January 2013 and January 2022, cases of fungemia caused by RYOC were retrospectively examined. Antifungal susceptibility tests were performed according to the Clinical and Laboratory Standards Institute M27-A3.

Results: The incidence of RYOC was %4,9 (n=31) among 637 fungemia episodes. The most common isolated fungi were *Trichosporon asahii* (n=11). An antifungal susceptibility test could be performed on 25/31 strains. Azole minimum inhibitory concentration (MIC) values were low for *T. asahii* and *T. coremiiforme*. Amphotericin-B and voriconazole (VRC) MICs were low for *Saprochaete clavata* isolates, whereas those of fluconazole (FLC) and echinocandin were high. The most commonly preferred empirical antifungal was liposomal amphotericin-B (n=7) followed by VRC (n=4) and FLC (n=2). Of the 13 patients who received appropriate treatment either started empirically or after identification, 10 survived (p=0.01). The overall mortality rate was 53% (n=16). The mortality rate of patients with hematologic malignancy was significantly higher than that other patients with risk factors (p=0.01). Of the patients in whom appropriate treatment was initiated, three died because the foci of infection could not be controlled.

Conclusion: Maintaining high clinical suspicion of RYOC is crucial in empirical treatment. Early detection of species and determining antifungal susceptibility patterns of RYOC will guide clinicians in the treatment of these yeasts.

Keywords: Fungemia, antifungal agents, invasive fungal infections

Öz

Giriş: *Candida* dışında görülen mayalar (CDGM)'a bağlı fungemi olguları literatürde artan oranda bildirilmektedir. , ancak bu hastaların yönetimine ilişkin veriler sınırlıdır. Bu çalışma, üçüncü basamak bir üniversite hastanesinde CDGM'ye bağlı fungemili hastaların klinik özelliklerini, yönetimini, sonuçlarını ve izolatlarının antifungal duyarlılık profillerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Ocak 2013 ile Ocak 2022 arasında CDGM'nin neden olduğu fungemi olguları retrospektif olarak analiz edildi. Antifungal duyarlılık testleri Klinik ve Laboratuvar Standartları Enstitüsü M27-A3'e göre yapıldı.

Bulgular: CDGM insidansı 637 fungemi atağı arasında %4,9 (n=31) idi. En sık izole edilen mantar *Trichosporon asahii* (n=11) idi. Suşların 25'ine antifungal duyarlılık testi yapılabildi. Azol minimum inhibitör konsantrasyon (MİK) değerleri *T. asahii* ve *T. coremiiforme* suşları için düşük bulunmuştur. *Saprochaete clavata* izolatlarında amfoterisin-B ve vorikonazol MİK değerleri düşük, flukonazol ve ekinokandin yüksek bulunmuştur. En sık tercih edilen ampirik antifungaller sırası ile lipozomal-amfoterisin-B (n=7), vorikonazol (n=4) ve flukonazoldur (n=2). Ampirik olarak veya tanımlandıktan sonra uygun tedaviye başlanan 13 hastanın 10'u hayatta kaldı (p=0,01). Mortalite %53 (n=16) idi. Hematolojik malignitesi olan hastaların mortalitesi

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Öz

diğer risk faktörlerine sahip hastalara göre anlamlı olarak yüksekti (p=0,01). Uygun tedavi başlanan hastalardan üçü enfeksiyon odağının kontrol altına alınamaması nedeni ile öldü.

Sonuç: Mantar enfeksiyonu için predispozan faktörleri olan hastalarda ampirik tedavide CDGM akılda bulundurulmalıdır. CDGM'nin erken tanısına ve antifungal duyarlılık paternlerine yönelik ileri çalışmalar, bu mayaların tedavisinde klinisyenlere yol gösterecektir.

Anahtar Kelimeler: Fungemi, antifungal ajanlar, invazif fungal enfeksiyonlar

Introduction

The epidemiology of invasive fungal infections (IFIs) has changed because of empirical antifungal treatment strategies in the growing population of patients with immunosuppression[1]. *Candida* spp. is the most common cause of IFIs worldwide (63-70%)[1]. However, rare yeasts other than *Candida* (RYOC) - *Saccharomyces, Saprochaete, Trichosporon, Cryptococcus, Rhodotorula*, and *Malassezia* spp. - are causing sporadic outbreaks over the past two decades[2-4]. The Infectious Diseases Society of America (2016) and European Conference on Infections in Leukemia-6 (2017) guidelines recommend the use of echinocandin as the first step in the management of fungemia[5,6]. However, the majority of RYOC have intrinsic resistance or decreased susceptibility to echinocandins[1,7]. Given the limited data on antifungal susceptibility patterns of rare yeasts and the paucity of susceptibility breakpoints, evidence for the management of these fungi is scarce[8]. Thus, this study aimed to determine the clinical characteristics of patients with bloodstream infection caused by RYOC, antifungal minimum inhibitory concentration (MIC) values of isolates, and effectiveness of antifungal treatments.

Materials and Methods

Between January 2013 and January 2022, cases of fungemia caused by RYOC were retrospectively examined, and data were collected from electronic records. Fungemia caused by rare yeasts was defined as RYOC isolated in one or more blood culture in patients with clinical signs of infection such as fever and/or sepsis. In patients who had fungemia more than once, the first culture was assessed. The presence of a central venous catheter (CVC), parenteral nutrition, history of antibiotic therapy, hospitalization in the intensive care unit (ICU), neutropenia, and history of surgery were accepted as risk factors of IFIs[9]. Neutropenia was defined as the absolute number of neutrophils of <500 cells/ml. Peripherally inserted central catheters and port catheters were considered CVCs. The administration of any antimicrobial drug in the month preceding the episode of fungemia was considered a previous antimicrobial exposure. Surgical operations performed within the last month were considered surgical history. In evaluating the appropriate antifungal therapy, the microorganisms, MIC values, and guideline recommendations were taken into consideration[7].

Clinical specimens were cultured on a Sabouraud dextrose agar (SDA) medium and were incubated for 24-48 h at 35 °C and 25 °C. Colonies formed in the SDA medium were identified using API-ID-20C-AUX (Bio-Merieux, Brussels, Belgium) and matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF) (Bruker Daltonics, Bremen, Germany) in addition to conventional methods. Owing to the widespread application of molecular technologies in taxonomy, fungal species have undergone a significant nomenclature change[10]. In this study, *Candida krusei, Candida kefyr, Saprochaete clavata,* and *Cryptococcus laurentii* were renamed to *Pichia kudriavzevii*, *Kluyveromyces marxianus*, *Magnusiomyces clavatus,* and *Papiliotrema laurentii,* respectively. *In vitro* susceptibility tests against amphotericin-B (AMB), fluconazole (FLC), itraconazole, posaconazole, voriconazole (VRC), caspofungin (CAS), micafungin, and anidulafungin were performed using Sensititre® YeastOne (TREK Diagnostic System, East Grinstead, UK) based on Clinical and Laboratory Standards Institute standards[11].

The study protocol was approved by the Clinical Research Ethics Committee of Karadeniz Technical University on April 29, 2022 (no: 2022-73), and study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics version 23.0 (IBM Corp., Armonk, NY, USA). Quantitative data were presented as mean±standard deviation or median with interquartile range (IQR). Fisher's exact test was used to compare the ratios of categorical variables. A p value <0.05 was considered significant.

Results

The demographic data and clinical characteristics of the patients are given in Table 1. *C. neoformans* were isolated in the blood cultures of two patients with acquired immunodeficiency syndrome. In our study, 637 fungemia cases were detected. Of these cases, %4,9 were caused by non-*Candida* yeasts. Among the isolated agents, 11 (35.5%) were *Trichosporon asahii*,

1 (3.2%) *Trichosporon coremiiforme*, 9 (29%) *Saprochaete clavata* (formerly *Geotrichum* spp.), 2 (6.5%) *Saccharomyces cerevisiae*, 4 (12.9%) *Cryptococcus neoformans*, 1 (3.2%) *Cryptococcus laurentii*, 2 (6.5%) *Rhodotorula rubra*, and 1 (3.2%) *Rhodotorula mucilaginosa*. No clustering was observed during the study period. In 15 of the patients, the growth of the same fungal species responsible for fungemia was isolated in clinical samples taken from other regions, i.e., four in urine samples, three in CVCs, 2 in cerebrospinal fluid (CSF), 1 each in the CVC and bronchoalveolar lavage (BAL), one each in the CSF and BAL, one in CVC, and one in the peritoneal culture.

The median time to the onset of fungemia was 16 (IQR=7-30) days of hospitalization. Data from 24 patients revealed that the median time to initial fungal growth in blood cultures during incubation was 120 h (IQR=84-137). In addition to RYOC, *Candida* spp. was isolated in blood cultures of eight patients (*C. albicans* in six, *C. krusei* in one, *C. kefyr* in one, and *C. parapsilosis* in one patient). Sixteen (53%) of the patients died. The median time from fungemia onset to death was 6 (IQR=3.5-9.5) days. The mortality rate of patients with hematologic malignancy was significantly higher than that in other patients with risk factors [p=0.01; Odds ratio (OR)=10.8; 95% confidence interval (CI): 1.79-65.55]. An antifungal susceptibility test could be performed on 25/31 (80%) strains. Since the susceptibility breakpoints for these species have not yet been determined, the distribution of MIC values for each tested antifungal is given in Table 2.

Table 1. Demographic and clinical characteristics of the patients with fungemia

	n=31	%
Mean age (±SD) (years)	44.6 (±23)	
Male sex	15	48%
Hematological malignancy	12	38%
Solid-organ tumors	5	16%
Cardiovascular diseases	3	9%
Diabetes mellitus	9	29%
Prior antimicrobial exposure	26	83%
Central venous catheter	22	70%
Total parenteral nutrition	21	67%
Intensive care unit stay	15	48%
Neutropenia [median 20 (IQR 10-45) days]	11	35%
History of surgery	7	22%
Mortality	16	51%

SD: Standard deviation, IQR: Interquartile range

Characteristics, antifungal susceptibilities, and antifungal management of patients with *Trichosporon* spp. fungemia are shown in Table 3. Of the 12 patients with *Trichosporon* spp. fungemia, four were followed up for solid-organ tumors. Among them, a 71-year-old male patient who was diagnosed with metastatic bladder cancer, yeast-isolated blood and nephrostomy culture was taken on day 15 of hospitalization, and VRC (MIC=0.03 µg/ml) was started. The nephrostomy could not be removed because of the patient's unstable clinical condition, and fungemia continued on day 5 of treatment. The patient died on day 7 of therapy. In a 73-year-old man with prostate cancer, *T. asahii* growth was reported in the blood and nephrostomy culture on day 24 of the ICU follow-up. The patient was started on VRC (MIC=0.03 µg/ml), and treatment was revised to liposomal amphotericin-B (L-AmB) (MIC=0.25 µg/ml) due to a decrease in the glomerular filtration rate, and he died on day 10 of therapy. In a 56-year-old woman with bilateral nephrostomy due to ovarian cancer, *T. asahii* was isolated in the blood and nephrostomy culture on day 10 of hospitalization, and she was started on VRC (MIC=1 µg/ml). After the nephrostomies were revised, the treatment was completed, and no relapse was observed. In a 77-year-old man with lung adenocarcinoma, yeast was isolated in his blood culture on day 22 of admission. Fluconazole was started, and *C. parapsilosis* (MIC=0.125 µg/ml) and *T. asahii* (MIC=2 µg/ml) were isolated in the blood culture.

Table 2. Minimum inhibitory concentration ranges (µg/ml) for each antifungal drug tested for rare yeast

Yeast species (n)	AMB*	FLC†	ITC‡	VRC§	POS‖	CAS¶	MFG**	AFG††
Trichosporon asahii (9)	0.25-2	2-4	0.12-0.25	0.03-1	0.12-0.5	8	8	8
Trichosporon coremiiforme (1)	1	1	0.12	0.015	0.06	8	8	8
Magnusiomyces clavatus (9) (formerly *Saprochaete clavata*)	0.5-1	4-32	0.06-2	0.06-1	0.12-1	2-8	0.5-4	1-2
Saccharomyces cerevisiae (1)	0.002	-	1	1	8	0.12	–	–
Rhodotorula rubra (2)	0.5	0.5-2	0.06-0.12	0.08-0.03	0.03	0.25-5	1	1
Rhodotorula mucilaginosa (1)	0.25	256	1	2	1	8	8	8
Cryptococcus neoformans (1)	0.12	2	<0.015	<0.015-0.08	0.015	8	8	8
Papiliotrema laurentii (1) (formerly *Cryptococcus laurentii*)	2	>256	>16	>8	>8	0.12	0.06	0.12

*Amphotericin-B, †Fluconazole, ‡Itraconazole, §Voriconazole, ‖Posaconazole, ¶Caspofungin, **Micafungin, ††Anidulafungin

The patient's urinary catheter and CVCs were removed, and he was on a 14-day regimen. In addition, a 44-year-old man was receiving broad-spectrum antibiotics for hospital-associated pneumonia due to multidrug-resistant microorganism in the ICU where he was followed for Coronavirus disease-2019. *T. asahii* was isolated in the blood and urine cultures taken on day 30 of hospitalization. The patient died before the growth in the blood culture was detected.

Saprochaete clavata was isolated in nine patients. Characteristics, antifungal susceptibilities, and antifungal management of the patients are shown in Table 4. Yeast was reported in the culture, and eight of the patients were receiving empirical antifungal therapy (CAS or L-AmB). Among them, a 16-year-old man with AML had fever on day 38 of L-AmB therapy, and blood cultures were taken in addition to oral mucosal biopsy. Voriconazole (MIC=0.12 µg/ml) was added to the treatment after *S. clavata* growth was detected. The patient, whose skin lesions progressed under treatment and clinical conditions worsened, died on day 4 of the revision.

Table 3. Characteristics, antifungal susceptibilities, and antifungal management of the patients with fungemia due to *Trichosporon asahii*

Age/ sex	Underlying diseases	Emprical treatment	Other sites from which fungi were isolaed	Antifungal susceptibility (µg/ml)						Treatment revision	Outcome
				AMB	FLC	ITC	VRC	POS	CAS		
18/F	Neurogenic bladder	AMB		–	–	–	–	–	–	VRC	Cure
65/F	ALL*	AMB		–	–	–	–	–	–	VRC	Exitus
71/M	Bladder cancer	VRC		1	2	0.12	0.03	0.12	8		Exitus
55/M	Renal transplantation	CAS		1	2	0.25	0.03	0.12	8	**	Exitus
73/M	Prostate cancer	VRC	CVC§& nephrostomy	1	2	0.12	0.03	0.12	8	AMB	Exitus
56/F	Ovarian cancer	VRC	Nephrostomy	0.5	4	0.12	1	0.25	0		Cure
32/F	AML†	AMB		1	2	0.12	0.03	0.12	8	AMB&VRC	Cure
77/M	Lung cancer	FLC		1	2	0.12	0.03	0.12	8		Cure
61/F	CRF‡			1	4	0.25	0.06	0.25	8	VRC	Cure
20/F	ALL	VRC		1	2	0.25	0.12	0.5	>8	VRC&AMB	Exitus
44/M	COVID-19		CVC	0.25	4	0.25	0	0.25	>8	**	Exitus

*Acute lymphoblastic leukemia, †Acute myeloid leukemia, ‡Chronic renal failure, §Central venous catheter, **Died before yeast-positive blood culture report.

F: Female, M: Male, VRC: Voriconazole, AMB: Amphotericin-B, CAS: Caspofungin, POS: Posaconazole, COVID-19: Coronavirus disease-2019

Table 4. Characteristics, antifungal susceptibilities, and antifungal management of patients with fungemia due to *Saprochaete clavata*

Age/Sex	Underlying disease	Emprical treatment	Other sites from which fungi were isolated	Antifungal susceptibility (µg/ml)						Treatment revision	Outcome
				AMB	FLC	ITC	VRC	POS	CAS		
18/F	ALL*	AMB	BAL‖	1	32	–	0.5	1	8	AMB and VRC	Exitus
52/F	AML†	AMB		1	16	0.25	0.25	0.5	8	AMB and VRC	Exitus
60/F	NHL‡	CAS	CVC¶	0.5	4	0.12	0.12	0.25	0	AMB and VRC	Exitus
63/F	Colon Ca§	–		1	32	–	0.5	1	8	AMB	Cure
17/M	AML	AMB	CVC and skin biopsy	0.5	16	0.25	0.12	0.25	2	AMB and VRC	Exitus
61/M	AML	CAS		0.5	16	0.25	0.25	0.5	8	**	Exitus
63/M	AML	CAS	CVC and BAL	0.5	8	2	0.5	1	4	AMB and VRC	Exitus
29/F	NHL	AMB		0.5	4	0.06	0.06	0.12	4	AMB and VRC	Exitus
42/F	AML	AMB		0.5	4	0.12	1	0.25	--	VRC	Exitus

*Acute lymphoblastic leukemia, †Acute myeloid leukemia, ‡Non-Hodgkin lymphoma, §Colon cancer, ‖Bronchoalveolar lavage, ¶Central venous catheter, **Died before yeast-positive blood culture report.

BAL: Bronchoalveolar lavage, F: Female, M: Male

Rhodotorula rubra was isolated in two patients: an 18-year-old man admitted in the ICU because of pneumonia. Empirical FLC was started due to *C. albicans* colonization in the urinary catheter, and fever was observed under broad-spectrum antibiotics. On day 7 of treatment, yeast was isolated in the CVC and blood, and treatment was revised as CAS (MIC=0.5 µg/ml). After the catheter removal, the patient was cured with 20-day antifungal regimen.

Two of the 15 patients who had not received empirical antifungal therapy died before yeast growth in the blood was detected. The most common preferred empirical antifungal was L-AmB (n=7), followed by VRC (n=4) and FLC (n=2). Of the 13 patients who received appropriate treatment either started empirically or after identification, 10 survived. Among 18 patients who did not receive appropriate treatment, only five survived (p=0.01, OR=8.67, 95% CI=1.66-45.2). Of the patients whom appropriate treatment was initiated, three died (in two patients, the infection focus could not be removed and one had disseminated infection).

Discussion

RYOC causes fungemia or disseminated infection mostly in patients with immunosuppressed status and those with risk factors. Therefore, determining the clinical features of patients and the local antifungal MIC values of RYOC strains will be helpful in patient treatment and management.

In the related literature, the incidence of RYOC-related fungemia differs between countries and centers. While this rate was 0.7% in a nationwide 8-year-surveillance report in Denmark, it was 1.8% in a multicenter study conducted in Spain[2,12]. In a study involving patients with cancer in the USA, this rate was determined as 2.1 cases per 100,000 patient days[13]. While this rate was 2.2% in a single-center study conducted in our country[14], a higher incidence rate (8.1%) was reported in a multicenter study from Asia[8]. In our study, the incidence of RYOC was 4,9%, similar to another study conducted in our country. Considering the predisposing factors, number of patients, and geographical conditions in various patient groups, different rates between centers are expected. In our study, the mortality rate of RYOC-related fungemia was 53%, which was consistent with recent reports. Yamamoto et al.[9] analyzed hospitalized adults and reported mortality rate of non-*Candida* fungemia of 54% (n=11), and Alp et al.[14] reported 47% (n=19). The duration of fungemia development after hospitalization was 16 days, and this period vary between 18 and 47 days in the literature[9,14]. The development time of fungemia was short in our center because of frequent hospitalizations due to chemotherapy protocols or comorbidity, as in 17 patients followed up with malignancies. Furthermore, eight of the 15 patients admitted in the ICU were transferred from an external center, making it difficult to make an objective assessment.

In accordance with population-based studies conducted in Denmark and France, the rare yeasts *Trichosporon* spp. and *Saprochaete clavata* were most commonly isolated at our center[2,6]. Moreover, the third most common pathogen isolated in our study was *Saccharomyces* spp., which was reported as the dominant species in the ARTEMIS study[15].

In recent years, *S. clavata* has attracted attention because of its increasing reports in patients with immunosuppressed status. It causes disseminated infection and is mostly reported in Mediterranean countries[16-19]. This fungus, which is resistant to echinocandins *in vitro*, has been reported in a case series of patients followed up with hematological malignancy[16,19,20]. Except one, all our patients with fungemia due to *S. clavata* had hematological malignancy. The antifungal susceptibility results of nine *S. clavata* isolates revealed low MICs for AMB and VRC, whereas FLC and echinocandin had high MIC values (Table 4). This microorganism, as reported in the literature, caused a breakthrough infection in five patients with hematological malignancies who received echinocandin therapy, and all patients died[21]. In our center, according to the guideline recommendations, L-AmB (AII) or CAS (AII) was preferred as empirical treatment in patients with hematological malignancies and fever under neutropenia[6]. Despite the revision of antifungal therapy to VRC and/or L-AmB initially or soon after having the identification and/or susceptibility test results, all patients with hematological malignancies died.

Biochemical tests often misidentify *S. clavata* as *S. capitata*. However, recent advances in pathogen analysis with MALDI-TOF have resulted in a high level of discrimination. *S. clavata* was detected in nine patients, and eight of these strains were identified in a previous study conducted in our hospital, consistent with nucleotide sequencing analysis with the MALDI-TOF MS biotyper 3.1 database[17]. In another study, patients with *S. capitata* fungemia were evaluated, and nine of 18 patients were successfully treated with L-AmB and VRC[3]. Although the MIC values reported in that study were similar to our values, the difference in mortality rates was thought to be related to the use of echinocandin in empirical treatment in our hospital. Moreover, *Saprochaete* spp. can cause disseminated infections with involvement of multiple organs such as the liver, spleen, lymph node, and bone marrow, leading to treatment failure and prolonged fungemia[20,21]. *S. clavata* was isolated in the tissue biopsy culture taken from the oral mucosa in one patient, and most of the patients with clinically unstable status could not be examined for visceral involvement. Thus, examination for systemic involvement is necessary in the management of patients with *S. clavata* fungemia.

Rhodotorula spp. can cause breakthrough infections even under CAS therapy[22]. Since *Rhodotorula* spp. is resistant to azole and echinocandin in vitro, AMB (AII) and flucytosine (AII) are recommended as first-line therapy[7]. In our case, when yeast was detected in the blood culture under FLC therapy, the treatment was revised to CAS. Considering the susceptibility test results (MIC=0.5 µg/ml), treatment was continued, and clinical and laboratory improvement was observed.

Azole MIC values were low for *T. asahii* and *T. coremiiforme* (Table 2). Two of the patients with *Trichosporon* spp. fungemia were treated with FLC (MIC=2 µg/ml) or VRC (MIC=1 µg/ml) with source control. Since *Trichosporon* spp. is resistant to AMB *in vitro*, VRC (BIII) is recommended as the first-line treatment in guidelines, and a study showed that FLC (CIII) can be used in the treatment[7]. In a study that reported successful treatment of *Trichosporon* spp. with VRC, higher MIC values were found for AMB, which is similar to our findings[2]. In a review, treatment failure was more common in patients on L-AmB, and significantly positive results were observed in patients who received a combination of VRC and/or L-AmB[23].

Study Limitations

The main limitation of this study is the small sample size owing to the low incidence and retrospective design. A comparison in treatment management could not be made because of the small number of patients and heterogeneity of the groups.

Conclusion

Guidelines recommend specific antifungal therapies for specific RYOC treatment; however, the management of many rare yeast infections requires an individualized approach. Further studies on the early detection and antifungal susceptibility patterns of RYOC will guide clinicians in the treatment of these yeasts.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Karadeniz Technical University on April 29, 2022 (no: 2022-73), and study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.T., E.Ö., Concept: F.A., Design: F.A., Data Collection or Processing: D.T., G.Y., Analysis or Interpretation: D.T., G.Y., İ.T., E.Ö., Literature Search: D.T., S.K., Writing: D.T., F.A., G.Y.

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