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ORIGINAL ARTICLE

Exploring oral candidiasis among cancer patients undergoing chemotherapy in eastern Iran

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ABSTRACT

Background and Objectives: Understanding the epidemiology of *Candida* species among cancer patients is crucial for preventing invasive infections. This study aimed to identify *Candida* species and assess risk factors among cancer patients receiving chemotherapy in Birjand, eastern Iran.

Materials and Methods: The samples were obtained from the oral cavity of 140 patients and the initial identification of *Candida* species was carried out through fungal cultures. Subsequently, *Candida* isolates were molecularly identified using the PCR-RFLP method with the restriction enzyme Msp1. Furthermore, the demographic characteristics, risk factors, and clinical history of the patients were extracted and scrutinized using a multiple logistic regression model.

Results: Among the 140 patients examined, 55 individuals (39.3%) tested positive for oral candidiasis (OC). Notably, Hemorrhagic cancer emerged as the most common type of cancer associated with OC (46.7%). The predominant species isolated was the *Candida albicans* complex (64.8%), followed by the *Candida glabrata* complex (26.8%). A noteworthy finding was the significant association between the occurrence of OC and the number of chemotherapy sessions ($P<0.05$). Conversely, no significant correlations were detected between OC and variables such as sex, age, type of cancer, occupation, residence, underlying disease, and drug use ($P>0.05$).

Conclusion: The prevalence of *Candida* spp. and its correlation with the number of chemotherapy sessions underscored the importance of preventive measures. These findings provided valuable insights for designing targeted interventions to mitigate the burden of oral candidiasis in this vulnerable population.

Keywords: Candidiasis; Neoplasms; Chemotherapy adjuvant; *Candida*; Risk factors; Epidemiology

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INTRODUCTION

Cancer represents as one of the most pressing global health challenges, leading to a significant number of fatalities each year. Current treatment modalities include surgery, radiation therapy, and chemotherapy. While surgery and radiation can be effective for localized tumors, systemic interventions like chemotherapy are essential for metastatic cancers (1, 2). However, chemotherapy often compromises the immune system and adversely affects patients' quality of life. The immunosuppression caused by chemotherapy, coupled with oral side effects such as mucosal inflammation and dry mouth, increases susceptibility to opportunistic infections (3, 4).

Candidiasis includes a wide range of conditions, varying from superficial mucocutaneous disorders to severe invasive diseases. Among the *Candida* species, *Candida albicans* is the predominant strain found in the normal oral flora. However, recent trends indicate a significant increase in non-*albicans Candida* species, particularly among individuals with cancer and immunodeficiency. This rise can be attributed to alterations in the oral microbiota, which are often driven by factors such as immune compromise and the effects of chemotherapy. These changes create an environment conducive to *Candida* colonization and increase the risk of developing oral mucositis (5).

Oral candidiasis is the most prevalent fungal infection in immunocompromised individuals, posing significant risks for cancer patients (6). If left untreated, mucosal candidiasis can escalate to life-threatening systemic infections. Various factors, including prolonged hospital stays, extensive antibiotic use, neoplastic conditions, immunosuppressive therapies, and intubation, contribute to the risk of candidemia (7). Chemotherapy can disrupt the balance of the oral microbiome through its effects on salivary secretion and the increased need for antibiotics, thereby compromising natural defense mechanisms against *Candida* overgrowth (8). This disruption can lead to the development of oral candidiasis which in patients experiencing severe and prolonged neutropenia may result in systemic candidiasis (9, 10). In oncology, where adherence to treatment and maintaining adequate nutritional intake are crucial, the presence of oral candidiasis can significantly affect systemic outcomes (11, 12). Due to the non-specific clinical manifestations and the lengthy diagnostic processes associated with systemic candidiasis, timely detection of mucosal colonization is critical for mitigating related risks (13).

Given the clinical importance of diagnosing oral candidiasis in cancer patients, it is crucial to understand the epidemiology and distribution of *Candida* species within this vulnerable population. Oral candidiasis can significantly impact treatment outcomes, and increased risk of systemic infections. This study aims to identify the specific *Candida* species present and assess the associated risk factors among cancer patients receiving chemotherapy in Birjand City, located in eastern Iran. By providing insights into the microbial aspect of oral candidiasis in this specific population, this investigation sought to enhance preventive strategies and optimize patient care in clinical settings. Furthermore, the findings may contribute to a broader understanding of the relationship between chemotherapy, oral health, and opportunistic infections, thereby informing researchers for future research and clinical practices.

MATERIALS AND METHODS

Study population. This descriptive cross-sectional study was conducted at Iranmehr Hospital in Birjand from April to November 2023, focusing on cancer patients undergoing chemotherapy. The research received approval from Birjand University of Medical Sciences, and the Code of Ethics (IR.BUMS.REC.445.1399) was obtained. The study's inclusion criteria specified patients who had not received antifungal or azole-prophylaxis before or during radiotherapy. Participants provided written consent and completed a questionnaire encompassing demographic information (such as sex, age, type of cancer, etc.), treatment specifics, and clinical history. Clinical symptoms observed in patients included dry mouth, altered taste perception, oral redness, presence of a white or cream-colored membrane, and a burning sensation. Oral candidiasis was defined to encompass both oral *Candida* colonization and infection (14). Oral candidiasis involved colony counting on CHROMagar *Candida* chromogenic medium with a threshold of more than 50 colonies (14, 15).

Culture of samples. Sampling was performed using sterile swabs to collect oral specimens, which were subsequently cultured on CHROMagar *Candi-*

da chromogenic medium (CHROMagar TM, Pioneer, Paris, France). The samples were incubated at 37°C for 48 to 72 hours to facilitate the growth of *Candida* species. Fungal growth, diversity, and colony counts were assessed every 24 hours during this incubation period. *Candida* species were identified based on the color of the colonies. Subsequently, the isolates were cultured for 24 hours at 35°C on Sabouraud Dextrose Agar (SDA) supplemented with chloramphenicol from Liofilchem (Italy) to achieve purification. The cultivated species were then transferred to a microtube containing distilled water for long-term storage before molecular examinations.

Molecular identification by ITS sequencing. The isolates were cultured on SDA medium for 48 hours at 28°C. The genomic DNA of the colonies was extracted utilizing the phenol-chloroform technique as described previously (16). The DNA extracts were subsequently preserved at -20°C until required for analysis. The specific primer sequences targeting the Internal Transcribed Spacer regions (ITS 1 and ITS 4) were as follows: 5'-TCC GTA GGT GAA CCT TGC GG-3' (forward) and 5'-TCC TCC GCT TAT TGA TAT GC-3' (reverse). The PCR amplification was performed under the following conditions: an initial denaturation step at 95°C for 1 minute, followed by 30 cycles of denaturation at 95°C for 60 seconds, annealing at 56°C for 60 seconds, extension at 72°C for 90 seconds, and a final extension at 72°C for 7 minutes. The resulting amplification products were separated by electrophoresis on a 1.2% agarose gel. To identify the species, the PCR product was cut using the restriction enzyme *Msp 1,* and the species were distinguished by analyzing the pattern of the cuts (17).

Data analysis. The data was analyzed by utilizing central and dispersion indicators, frequency tables, and appropriate diagrams. To ensure the normal distribution of quantitative variables, the Kolmogorov-Smirnov test was conducted. For normally distributed variables, the independent t-test was employed to calculate the average between the two groups; otherwise, the nonparametric Mann-Whitney test was utilized. The relationship between qualitative variables was assessed using the chi-square test and Fisher's exact test. Furthermore, the multiple logistic regression model was applied to identify factors associated with the prevalence of oral candidiasis infection. All analyses were performed using SPSS software version 20, with a significance level set at $p < 0.05$.

Ethical approval. The research project was approved by Birjand University of Medical Sciences, and the Code of Ethics was subsequently issued (IR.BUMS.REC.445.1399). In adherence to research ethics principles, written informed consent was obtained from every individual involved in the study.

RESULTS

Out of the 140 patients undergoing chemotherapy for different types of cancer, 60 (42.85%) were male and 80 (57.15%) were female. The patients' ages varied from 16 to 83 years, with an average age of 51.34 ± 14.79 years. The study revealed that 55 patients (39.3%) tested positive for oral candidiasis, with a prevalence rate of 38.8% among women and 40% among men. There was no statistically significant difference in the prevalence of oral candidiasis between genders ($p=0.88$). However, individuals aged over 60 exhibited a significantly higher prevalence of the infection (52%) compared to those under 60 (33%) ($p=0.02$). Among the participants, 72% resided in urban areas, while 28% lived in rural regions. The chi-square test results revealed no significant association between the patients' residential status and positive oral candidiasis cases ($p=0.61$). Furthermore, no significant correlation was observed between the prevalence of oral candidiasis and various factors such as occupation, smoking habits, and substance use ($p < 0.05$) (Table 1).

The study findings highlighted that the most common cancer types associated with oral candidiasis were hemorrhagic cancer (46.7%), breast cancer (44.1%), gastrointestinal tract cancer (40%), and other malignancies (31.7%). Nevertheless, the generalized Fisher's test indicated that there was no significant correlation between the type of cancer and the prevalence of oral candidiasis ($p>0.64$) (Table 2). The statistical analysis revealed a significant difference in the mean number of chemotherapy sessions and the prevalence of oral candidiasis ($p<0.008$). Conversely, no significant association was found between the prevalence of oral candidiasis and factors such as prosthetic treatment, surgical history, duration of chemotherapy, hospitalization history, and type of chemotherapy ($p<$

Table 1. Demographic characteristics and prevalence of oral candidiasis among cancer patients undergoing chemotherapy

Variables		Total	Results		P-value
			Negative	Positive	
Age (years)					
	Standard deviation ± mean	51/34 ± 14/79	52/73 ± 15/20	49.18 ± 13.99	P= 0.16
	≥ 60	94 (100)	63 (67)	31 (33)	P= 0.02*
	< 60	46 (100)	22 (47.8)	24 (52.2)	
Gender					
	Female	80 (100)	49 (61.2)	31 (38.8)	P= 0.88
	Male	60 (100)	36 (60)	24 (40)	
Location					
	City	101 (100)	60 (59.4)	41 (40.6)	P= 0.61
	Village	39 (100)	25 (64.1)	14 (35.9)	
Occupation					
	Housewife	57 (100)	32 (56.1)	25 (43.9)	
	Employee or retired	27 (100)	17 (63)	10 (37)	P= 0.65
	Other	56 (100)	36 (64.3)	20 (35.7)	
Smoking					
	No	132 (100)	80 (60.6)	52 (39.4)	P= 0.99
	Yes	8 (100)	5 (62.5)	3 (37.5)	
Drug use					
	No	107 (100)	67 (62.6)	40 (37.4)	P= 0.40
	Yes	33 (100)	18 (54.5)	15 (45.5)	

* Significant at the 0.05 level values are reported as number (percentage) or mean ± standard deviation

0.05) (Table 2).

In this study, the multiple logistic regression model was employed to determine the factors associated with the prevalence of oral candidiasis (Table 3). The findings of this analysis unveiled that solely the number of chemotherapy cycles exhibited a significant correlation with the prevalence of fungal infection ($p<0.05$). More precisely, the likelihood of contracting a fungal infection escalated by 7% for every incremental unit in the number of chemotherapy cycles, which was statistically significant ($p<0.05$) (Table 3).

In the current study, PCR-RFLP was utilized for the identification of the *Candida* species (Fig. 1). A total of 71 isolates were collected from the patients, comprising 46 (64.8%) from the *Candida albicans* complex and 25 (35.2%) from non-*albicans Candida* species. The distribution of isolated species in this study encompassed 46 (64%) cases of *C. albicans* complex, 19 (26.8%) cases of *C. glabrata*, 3 (4.2%) cases of *C. krusei*, 2 (2.8%) cases of *C. kefyr*, and 1 (1.4%) case of *C. tropicalis*. Notably, *C. glabrata* emerged as the most frequently isolated species among non-*albicans Candida* cases.

DISCUSSION

Oral candidiasis represents a significant health threat to immunocompromised patients, particularly those with malignancies undergoing chemotherapy (11). In our study, we identified that 55 out of 140 cancer patients (39.3%) were affected by oral candidiasis, underscoring the urgent need for effective monitoring and preventive strategies within this vulnerable population. This prevalence rate is significantly higher than the 21.3% reported by Maherolnaqsh et al. among cancer patients in Ahvaz (18). Furthermore, a study by Sabbar et al. revealed an alarming 76.8% positivity rate for oral candidiasis among cancer patients exhibiting suspicious oral symptoms (19). These findings highlight the critical necessity for routine oral examinations and proactive oral health assessments in cancer patients, particularly those undergoing intensive chemotherapy regimens. The discrepancies observed in prevalence rates across studies may be attributed to various factors, including the specific characteristics of the study populations, the types of cancers involved, the

Table 2. Comparison of prevalence of oral candidiasis in cancer patients undergoing chemotherapy according to other risk factors

Variables		Total	Results		P-value
			Negative	Positive	
Number of chemotherapy (Standard deviation ± mean)		9.56 ± 7.7	8.41 ± 7.45	11.33 ± 7.8	0.008*
Oral prosthesis					
	No	105 (100)	63 (60)	42 (40)	0.76
	Yes	35 (100)	22 (62.9)	13 (37.1)	
Underlying disease (At least one)	No	78 (100)	51 (65.4)	13 (37.1)	0.20
	Yes	62 (100)	34 (54.8)	28 (45.2)	
History of surgery					
	No	31 (100)	16 (51.6)	15 (48.4)	0.25
	Yes	108 (100)	68 (63)	40 (37)	
Type of cancer					
	Breast cancer	34 (100)	19 (55.9)	15 (44.1)	
	Gastrointestinal cancer	50 (100)	30 (60)	20 (40)	0.64
	Hematologic cancer	15 (100)	8 (53.3)	7 (46.7)	
	Other	41 (100)	28 (68.3)	13 (31.7)	
Hospitalization					
	No	111 (100)	67 (60.4)	44 (39.6)	0.86
	Yes	29 (100)	18 (62.1)	11 (37.9)	
Type of chemotherapy					
	Injection	131 (100)	80 (61.1)	51 (38.9)	0.73
	Injection-oral	9 (100)	5 (55.6)	4 (44.4)	
Duration of chemotherap ۲ (Year)	2 ≥	101 (100)	65 (64.4)	36 (35.6)	0.15
	2 <	39 (100)	20 (51.3)	19 (48.7)	

* Significant at the 0.05 level values are reported as number (percentage) or mean ± standard deviation

Table 3. The multiple logistic regression model to determine the factors related to the prevalence of oral candidiasis in cancer patients undergoing chemotherapy

Variable (base level)		OR (95% confidence interval)	P-value
Number of chemotherapy		1.07 (1.01-1.12)	0.01*
Age			
	(≤60)	2.00 (0.85-4.66)	0.10
	>60		
Duration of chemotherapy			
	(2 ≥)	1.40 (0.62-3.15)	0.41
	2<		
Underling disease			
	No	1.89 (0.86-4.14)	0.11
	Yes		
Type of cancer (Breast cancer)			
	Gastrointestinal cancer	1.05 (0.41-2.68)	0.91
	Hematologic cancer	1.40 (0.38-5.16)	0.60
	Other	0.63 (0.23-1.72)	0.37

* Significant at the 0.05 level values

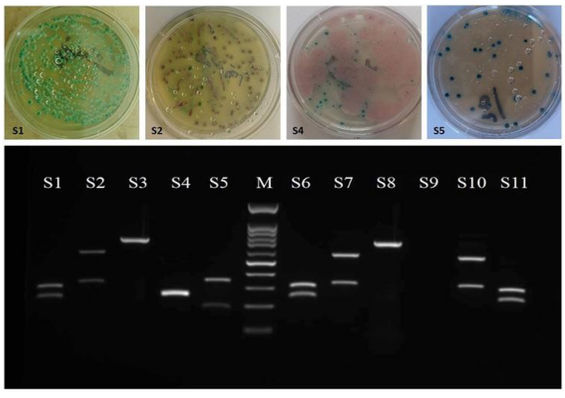

Fig. 1. Electrophoresis of PCR products of the ITS1-ITS2 region of *Candida* clinical isolates after enzymatic digestion with Msp l (M marker = 100bp, numbers 1-11: patient samples) (S1: *Candida albicans* complex (bp 239-298) (green colonies on CHROMagar medium), S2: *C. glabrata* complex (bp 320 and 541) (purple colonies on CHROMagar medium), S3: *C. kefir* (bp 720), S4: *C. krusei* (bp 250 and 260) (soft pink colonies on CHROMagar medium), S5: *C. tropicalis* (bp 186 and 340) (blue colonies on CHROMagar medium), M: marker, S6: *C. albicans*, S7: *C. glabrata*, S8: *C. kefir*, S9: negative control, S10: *C. glabrata*, S11: *C. albicans*).

duration and intensity of chemotherapy treatments, age demographics, and other relevant variables (20). The substantial prevalence of oral candidiasis among individuals with malignancies receiving chemotherapy poses a serious health threat. This increased susceptibility not only compromises the quality of life for these patients but also significantly elevates the risk of developing invasive candidiasis, a severe bloodstream infection that can lead to life-threatening complications such as sepsis, organ failure, and even mortality (21).

A key finding of our study is the significant correlation between age and the incidence of oral candidiasis, with patients aged 60 and above showing a markedly higher prevalence. This aligns with existing literature, including the study by Maherolnaghsh et al., which identified a 62.2% risk of *Candida* infection in older individuals. The aging process can compromise immune function, making older patients more susceptible to infections (18). This emphasizes the necessity for targeted preventive measures for elderly cancer patients, who may require closer monitoring and proactive management to mitigate the risk of oral candidiasis. Our study found no significant association between gender and the prevalence of oral candidiasis, corroborating the findings of Ma'amon et al. This suggests that factors other than gender may play a more substantial role in the development of oral candidiasis among cancer patients (22).

Moreover, we observed no significant relationships between oral candidiasis and lifestyle factors such as smoking and substance abuse. This contrasts with findings from Khedri et al., who reported a notable link between these risk factors and increased candidiasis incidence (23). Both smoking and substance abuse are recognized for their potential to disturb the normal oral flora, induce changes in the oral epithelium, and compromise the innate immune response. Consequently, individuals engaging in these practices are at a heightened susceptibility to opportunistic fungal infections like oral candidiasis (24). The absence of significant associations in our study may be due to the limited representation of smokers and substance abusers among our participants.

Our results indicated that patients with hematologic cancers had the highest prevalence of oral candidiasis. This finding is consistent with Nasri et al., who reported similar trends, particularly in patients with chronic lymphoid leukemia and lymphoma (25). Hematologic cancers, which include malignancies affecting the blood or bone marrow such as leukemia, lymphoma, and multiple myeloma, typically require more intensive chemotherapy regimens compared to solid tumors. The aggressive nature of these treatments often leads to significant immunosuppression, resulting in an increased susceptibility to infections, including candidiasis. The immunocompromised state induced by both the cancer itself and the associated therapies diminishes the body’s ability to combat fungal pathogens, creating an environment where oral candidiasis can thrive (26).

The study results revealed a significant correlation between the frequency of chemotherapy treatment cycles and the incidence of oral candidiasis. This finding is consistent with the observations made by Maherolnaqsh et al., who identified both chemotherapy and radiotherapy as significant risk factors for the development of candidiasis, further supporting the conclusions of the current investigation (18). Previous research has established that chemotherapy disrupts the body’s mucosal defenses, leading to conditions such as neutropenia, which significantly heightens the risk of candidiasis onset (27). Chemotherapy not only induces neutropenia characterized by a reduced number of neutrophils, a crucial com-

ponent of the immune response but also diminishes salivary flow, which plays a vital role in maintaining oral health. The reduction in saliva can compromise the oral mucosa's integrity and its ability to flush out pathogens, thereby creating a conducive environment for opportunistic infections like oral candidiasis (28, 29).

In this study, we isolated 71 strains from 140 patients, with 46 strains (64.8%) belonging to the *Candida albicans* complex and 25 strains (35.2%) classified as non-*albicans Candida*. Among the non-*albicans* species, *C. glabrata* was the most frequently identified, followed by *C. krusei*, *C. kefyr*, and *C. tropicalis.* These findings are consistent with existing literature, which indicated a higher prevalence of *C. albicans* compared to non-*albicans* species (28, 30). For instance, a study by Mousavi et al. investigated the *Candida* species involved in the oral colonization of 139 Iranian AIDS patients. The results revealed that 82.2% of the patients were colonized by *C. albicans*, while 17.8% harbored non-*albicans Candida* species. Among the latter, the *C. glabrata* complex emerged as the most prevalent, accounting for 7.29% of the cases (31). Recent studies have suggested a rising trend in the incidence of non-*albicans Candida* species causing oral candidiasis, despite *C. albicans* traditionally being recognized as the predominant causative agent in numerous investigations (32). This shift in prevalence from *C. albicans* to non-*albicans Candida* species may be influenced by various factors, including geographical variations, host immune status, antifungal resistance, and the use of catheters and intravenous nutrition in hospitalized patients (32). A meta-analysis of drug resistance in cancer patients indicated that *C. krusei* exhibited the highest resistance (pooled effect size = 0.85, $P < 0.05$) and demonstrated a sensitivity-dose-dependent response to fluconazole (pooled effect size = 0.008, $P < 0.05$). As a result, non-albicans *Candida* species displayed a higher rate of antifungal resistance compared to *C. albicans* ($P < 0.05$) (32). Additionally, an analysis of the susceptibility profiles of 45 *Candida* isolates to nine common antifungal agents including amphotericin B, itraconazole, voriconazole, fluconazole, nystatin, clotrimazole, caspofungin, micafungin, and anidulafungin conducted by Nasri et al. demonstrated that the geometric mean (GM) fluconazole minimum inhibitory concentration (MIC) values for non-*albicans Candida* species were significantly higher than those for *C. albicans* isolates (3.1 vs. 0.42 µg/ml). Notably, all isolates resistant to fluconazole (8.8%) were identified as non-*albicans Candida* species (25). These findings underscore the importance of ongoing surveillance of *Candida* species and their antifungal susceptibility profiles, particularly in vulnerable populations such as cancer patients, to inform treatment strategies and improve patient outcomes.

A limitation of this study was the small number of patients undergoing chemotherapy for specific types of cancer, particularly certain hematologic malignancies. To address this limitation, it is recommended that future studies be conducted as multicenter research involving diverse geographical areas. Multicenter studies could facilitate the exploration of regional variations in *Candida* species distribution and antifungal resistance patterns, ultimately contributing to more effective prevention and treatment strategies.

CONCLUSION

The current study revealed a noteworthy prevalence of oral candidiasis among cancer patients undergoing chemotherapy in the eastern region of Iran. Our investigation demonstrated a strong correlation between the number of chemotherapy sessions and the incidence of oral infections, indicating that patients treated primarily with chemotherapy are particularly vulnerable to these complications. Notably, the *C. glabrata* complex emerged as the most prevalent non-*albicans Candida* species among the patients studied. Given the resistance of non-*albicans Candida* species to antifungal treatments, these findings are crucial for health policies focused on preventing invasive candidiasis and developing effective treatment strategies for this condition.

REFERENCES

1. Li C, He WQ. Comparison of primary liver cancer mortality estimates from World Health Organization, global burden disease and global cancer observatory. *Liver Int* 2022; 42: 2299-2316.
2. Demaria S, Golden EB, Formenti SC. Role of local radiation therapy in cancer Immunotherapy. *JAMA Oncol* 2015; 1: 1325-1332.
3. Chaveli-López B. Oral toxicity produced by chemother-

apy: A systematic review. *J Clin Exp Dent* 2014; 6(1): e81-e90.
4. Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *Lancet Infect Dis* 2015; 15: 1429-1437.
5. Bunetel L, Tamanai-Shacoori Z, Martin B, Autier B, Guiller A, Bonnaure-Mallet M. Interactions between oral commensal *Candida* and oral bacterial communities in immunocompromised and healthy children. *J Mycol Med* 2019; 29: 223-232.
6. Lalla RV, Latortue MC, Hong CH, Ariyawardana A, D'Amato-Palumbo S, Fischer DJ, et al. A systematic review of oral fungal infections in patients receiving cancer therapy. *Support Care Cancer* 2010; 18: 985-992.
7. Charsizadeh A, Nikmanesh B, Ahmadi B, Jalalizand N, Jafari Z, Rahmani M, et al. Frequency of *Candida* species isolated from patients in children's Medical Center, Tehran, Iran. *Arch Pediatr Infect Dis* 2017; 6(1): e62410.
8. Puri S, Edgerton M. How does it kill?: understanding the candidacidal mechanism of salivary histatin 5. *Eukaryot Cell* 2014; 13: 958-964.
9. Mendonça MA, Cunha FQ, Murta EF, Tavares-Murta BM. Failure of neutrophil chemotactic function in breast cancer patients treated with chemotherapy. *Cancer Chemother Pharmacol* 2006; 57: 663-670.
10. Saloustros E, Tryfonidis K, Georgoulias V. Prophylactic and therapeutic strategies in chemotherapy-induced neutropenia. *Expert Opin Pharmacother* 2011; 12: 851-863.
11. Westbrook SD, Kirkpatrick WR, Wiederhold NP, Freytes CO, Toro JJ, Patterson TF, et al. Microbiology and epidemiology of oral yeast colonization in hemopoietic progenitor cell transplant recipients. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; 115: 354-358.
12. Abastabar M, Shokohi T, Kord RR, Badali H, Hashemi SJ, Ghasemi Z, et al. *In vitro* activity of econazole in comparison with three common antifungal agents against clinical *Candida* strains isolated from superficial infections. *Curr Med Mycol* 2015; 1: 7-12.
13. Zaoutis TE, Prasad PA, Localio AR, Coffin SE, Bell LM, Walsh TJ, et al. Risk factors and predictors for candidemia in pediatric intensive care unit patients: implications for prevention. *Clin Infect Dis* 2010; 51(5): e38-e45.
14. Rafat Z, Sasani E, Salimi Y, Hajimohammadi S, Shenagari M, Roostaei D. The prevalence, etiological agents, clinical features, treatment, and diagnosis of HIV-associated oral Candidiasis in pediatrics across the world: A systematic review and meta-analysis. *Front Pediatr* 2021; 9: 805527.
15. Gadducci A, Cosio S. Neoadjuvant chemotherapy in locally advanced cervical cancer: review of the literature and perspectives of clinical research. *Anticancer Res* 2020; 40: 4819-4828.
16. Kord M, Salehi M, Khodavaisy S, Hashemi SJ, Daie Ghazvini R, Rezaei S, et al. Epidemiology of yeast species causing bloodstream infection in Tehran, Iran (2015–2017); superiority of 21-plex PCR over the Vitek 2 system for yeast identification. *J Med Microbiol* 2020; 69: 712-720.
17. Mirhendi H, Makimura K, Khoramizadeh M, Yamaguchi H. A one-enzyme PCR-RFLP assay for identification of six medically important *Candida* species. *Nihon Ishinkin Gakkai Zasshi* 2006; 47: 225-229.
18. Maheronnaghsh M, Fatahinia M, Dehghan P, Teimoori A. Identification of *Candida* species and antifungal susceptibility in cancer patients with oral lesions in Ahvaz, Southern West of Iran. *Adv Biomed Res* 2020; 9: 50.
19. Sabar KA, Abdulbaqi NJ. Isolation of *Candida* spp. from cancer patients who suffered oral candidiasis due to immunodeficiency. *Plant Arch* 2020; 20: 1222-1224.
20. Alnuaimi AD, Wiesenfeld D, O'Brien-Simpson NM, Reynolds EC, McCullough MJ. Oral *Candida* colonization in oral cancer patients and its relationship with traditional risk factors of oral cancer: a matched case-control study. *Oral Oncol* 2015; 51: 139-145.
21. Armstrong-James D, Meintjes G, Brown GD. A neglected epidemic: fungal infections in HIV/AIDS. *Trends Microbiol* 2014; 22: 120-127.
22. Rawashdeh MA, Ayesh JA, Darwazeh AM. Oral candidal colonization in cleft patients as a function of age, gender, surgery, type of cleft, and oral health. *J Oral Maxillofac Surg* 2011; 69: 1207-1213.
23. Khedri S, Santos ALS, Roudbary M, Hadighi R, Falahati M, Farahyar S, et al. Iranian HIV/AIDS patients with oropharyngeal candidiasis: identification, prevalence and antifungal susceptibility of *Candida* species. *Lett Appl Microbiol* 2018; 67: 392-399.
24. Ye P, Chen W, Huang F, Liu Q, Zhu Y-N, Wang X, et al. Smoking increases oral mucosa susceptibility to *Candida albicans* infection via the Nrf2 pathway: In vitro and animal studies. *J Cell Mol Med* 2021; 25: 7948-7960.
25. Nasri E, Vaezi A, Falahatinejad M, Rizi MH, Sharifi M, Sadeghi S, et al. Species distribution and susceptibility profiles of oral candidiasis in hematological malignancy and solid tumor patients. *Braz J Microbiol* 2023; 54: 143-149.
26. Lanier OL, Pérez-Herrero E, Andrea APD', Bahrami K, Lee E, Ward DM, et al. Immunotherapy approaches for hematological cancers. *iScience* 2022; 25: 105326.
27. Hamzehee S, Kalantar-Neyestanaki D, Mohammadi MA, Nasibi S, Mousavi SAA. Identification of *Candi-*

da spp. isolated from oral mucosa in patients with leukemias and lymphomas in Iran. *Iran J Microbiol* 2019; 11: 114-119.

28. Souza E Silva VC, Oliveira VC, Sousa ÁFL, Bim FL, Macedo AP, Andrade D, et al. Prevalence and susceptibility profile of *Candida* spp. isolated from patients in cancer therapy. *Arch Oral Biol* 2020; 119: 104906.
29. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. *Cancer* 2004; 100: 228-237.
30. Ghojoghi A, Khodavaisy S, Mahmoudabadi AZ, Nazar E, Fatahinia M. Exploring the diversity of uncommon oral yeast species and associated risk factors among substance abusers in southwestern Iran. *Sci Rep* 2024; 14: 1906.
31. Mousavi SAA, Salari S, Rezaie S, Nejad NS, Hadizadeh S, Kamyabi H, et al. Identification of *Candida* species isolated from oral colonization in Iranian HIV-positive patients, by PCR-RFLP method. *Jundishapur J Microbiol* 2011; 5: 336-340.
32. Ghojoghi A, Erfaninejad M, Ahmadpour E, Nazar E, Barac A, Fatahinia M. Non-albicans candidemia in cancer patients as an increasing health problem: A comprehensive review and meta-analysis. *Asian Pac J Trop Med* 2022; 15: 387-399.