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Identification of *Candida* Species Isolated from Hospitalized Patients with Candiduria

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ABSTRACT

Background and objectives: The incidence of candiduria caused by *Candida* spp. has increased in recent years, particularly in hospitalized patients. Candiduria is most commonly caused by *Candida albicans*; however, an increase in the prevalence of non-*albicans* species has been observed during last decades. This study aimed at molecular identification of *Candida* species isolated from candiduria in hospitalized patients.

Methods: This cross-sectional study was conducted on 530 hospitalized patients in two hospitals in the Mazandaran Province, Iran. Midstream urine specimens were collected and then cultured on CHROMagar *Candida* medium. Molecular identification of common *Candida* species was carried out using the polymerase chain reaction-restriction fragment length polymorphism method after enzymatic digestion with *MspI*. *C. albicans* and *Candida parapsilosis* species complexes were identified by amplification of the *HWP1* and intein-containing vacuolar ATPase precursor genes, respectively.

Results: The frequency of candiduria was estimated at 14% among hospitalized patients. Of 74 samples positive for candiduria, 65 (87.8%) were isolated from females. The most common predisposing factor to candiduria was diabetes (n=36; 48.6%). The most frequent isolates were *C. albicans* complex (n=44; 59.4%), followed by *Candida glabrata* (n= 16; 21.6%), *Candida tropicalis* (n= 10; 13.5%), *Candida Krusei* (n= 3; 4%) and *C. parapsilosis* (n= 1; 1.3%).

Conclusion: Based on the results, the conventional and molecular methods produced similar results for identification of *Candida* species. However, accurate identification of *Candida* spp. requires the use of molecular techniques such as PCR-RFLP, *HWP1*, and intein-containing vacuolar ATPase precursor genes. Nevertheless, chromogenic methods such as CHROMagar *Candida* can be used for diagnosis of *Candida* spp. in laboratories with limited resources.

Keywords: *Candida*, PCR-RFLP, Candiduria, Hospitalized Patients.

INTRODUCTION

In recent decades, *Candida* species, which are known as opportunistic pathogens, have been reported as the fourth leading cause of bloodstream infections in hospitalized patients (1). Candiduria is defined as the presence of yeast in urine samples that indicates sample contamination, colonization of *Candida*, or urinary tract infections (UTI), such as disseminated candidiasis (2). Candiduria is confirmed when 10^4-10^5 CFU/ml (colony forming unit/ml of urine) of *Candida* is detected in urine; however, *Candida*-associated UTI is mostly determined by $>10^5$ CFU/ml and generally related to the symptoms of the patient (3). Among *Candida* species, *Candida albicans* has been reported as the most common cause of candiduria. Nevertheless, an increase in the rate of non-albicans species such as *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida kefir*, *Candida lusitanae*, *Candida guilhermondi*, and *Candida dubliniensis* has been reported during the last decades (4-6).

There is some evidence indicating that *Candida auris*, an emerging multidrug-resistant yeast was recently isolated from the urine of a hospitalized patient with candidemia (7). Therefore, accurate identification of species is very important for proper treatment. For example, some *Candida* species including *Candida krusei* and *C. glabrata* show intrinsic resistance to fluconazole. Predisposing factors of candiduria and *Candida* UTI include old age, female sex, diabetes mellitus, long hospital stay, admission to intensive care unit (ICU) , using broad-spectrum antibiotics, immunosuppressive therapy, radiation therapy, genitourinary tuberculosis, neutropenia, urinary tract instrumentation, renal defect, transplantation, abnormalities of the urinary tract, and catheterization (8,9). The incidence of candiduria caused by *Candida* spp. has increased in recent years, particularly in hospitalized patients. Depending on the clinical conditions and underlying diseases, the infection should be treated with effective antifungal agents (2, 10). More than 20% of hospitalized patients admitted to the ICU may develop candiduria following invasive therapeutic and diagnostic procedures (11, 12). Many studies demonstrated that candiduria in critically-ill ICU patients is a sign of severe colonization in the patients (13). Recently, *Candida* has been reported as the most common nosocomial pathogen isolated from the urogenital tract of ICU patients (14). The prevalence of candiduria in ICU patients was reported to be 19-44% (15). In a study in Spain, 22% of patients who stayed more than seven days in ICU developed candiduria. Approximately one third of ICU patients with a positive *Candida* culture had a urinary catheter. It has been also reported that ICU patients who receive four different antibiotics have 35% increased risk of developing candidiasis. If C*andida* is isolated from clinical specimens such as urine, the risk increases to 80% (16).

Candiduria can sometimes lead to systemic infection and candidiasis. Candidemia following candiduria that is associated with high morbidity and mortality (17). Most UTIs are caused by bacterial agents and *Candida* is often ignored, while increasing evidence suggest the increased rate of UTI cases caused by *Candida* species, especially in critically-ill patients (18, 19). The present study aimed at molecular identification of *Candida* species isolated from hospitalized patients with candiduria.

MATERIAL AND METHODS

This cross-sectional study was conducted at some hospitals in the Mazandaran Province, Iran, from May 2018 to April 2019. The study was approved by Ethics Committee of Islamic Azad University of Sari (ethical code: IR.IAU.SARI.REC.1399.051). A total of 530 patients in two hospitals of Imam Khomeini in Sari and Boo Ali Sina in Neka were enrolled. After obtaining informed consent, information including age, gender, hospital ward, duration of hospitalization, and history of diabetes mellitus, urinal catheter use, antimicrobial therapy, malignancies, and chronic obstructive pulmonary disease (COPD) were collected using a questionnaire. History of antifungal medications use and unwillingness to participate in the study were the exclusion criteria.

Midstream urine specimens were obtained after instructing patients on how to collect the sample to eliminate contamination. The specimens were immediately transferred to laboratory for analysis. The specimens were centrifuged at 3000 rpm for 3 minutes and sediment was examined under a microscope. Specimens containing yeast were subjected to

culture. Using a standard calibrated loop (0.01 ml), each un-centrifuged and homogenized urine specimen was cultured on CHROMagar *Candida* medium (CHROMagar Microbiology, France) and incubated at 35 °C for 24-48 hours aerobically away from light. Next, yeasts were primarily identified according to colony morphology. The number of colonies on each plate was counted and presence of $\geq 10^4$ CFU/ml *Candida* spp. in positive urine cultures was considered as candiduria (33).

All *Candida* spp. were subcultured on sabouraud dextrose agar (Merck, Germany), and genomic DNA was extracted from all recovered yeasts isolates according to a previously described method (20). Molecular identification of common *Candida* species was performed by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method (21). Briefly, the ITS1-5.8S rDNA-ITS2 region was amplified using the primers ITS1 (5'- TCC GTA GGT GAA CCT GCG G-3') and ITS4 (5'-TCC TCC GCT TAT TGA TAT GC-3'). The PCR amplification process was conducted as follows: initial denaturation at 95 ºC for 5 minutes, followed by 35 cycles of denaturation at 95 ºC for 15 seconds, annealing at 56 ºC for 30 seconds, and elongation at 72 ºC for 30 seconds.

The PCR products were digested with 5 units of the restriction enzyme *Msp*I (Fermentas, Vilnius, Lithuania) following gel electrophoresis on 2% agarose gel. *C. albicans* and *C. parapsilosis* species complexes were identified by amplification of the *HWP1* (Hyphal wall protein1) and intein-containing vacuolar ATPase precursor genes, respectively (22, 23) (Table 1).

Data were expressed by descriptive statistics including mean, standard deviation, frequency, and percentage. Data analysis was carried out using SPSS software (version 21).

Table 1- Primer sequences used for molecular identification of *Candida* isolates

Primer	Sequences (5'>3')	References
PCR-RFLP for all isolates		**(45)**
ITS1-Forward	**3'-GCACCTTCAGTCGTAGAGACG-5'**	
ITS4-Reverse	**3'-GCACCTTCAGTCGTAGAGACG-5'**	
***Candida albicans* species complex**		**(22)**
HWP1-Forward	**5'-GCTACCACTTCAGAATCATCATC-3′**	
HWP1-Reverse	**5'-GCACCTTCAGTCGTAGAGACG-3'**	
***Candida parapsilosis* species complex**		**(23)**
OM-Forward	**5'-GAGAAAGCACGCCTCTTTGC-3'**	
OM-Reverse	**5'-TCAGCATTTTGGGCTCTTGC-3'**	

RESULTS

None of the patients had treatment or prophylaxis with antifungal drugs. Out of 530 urine specimens, 74 (14%) were positive for candiduria with a colony count of $\geq 10^4$ CFU/ml. Of these samples, 65 (87.8%) were taken from females.

The mean age of patients with candiduria was 57.5 years (range 14–85 years). The highest rate of Candida spp. was observed in patients aged 41-70 years (Table 2).

Table 2- Age distribution of patients stratified by sex

Age (Years)	Male	Female	Total number (%)
11-20	**1**	**1**	**2 (2.7%)**
21-30	**0**	**8**	**8 (10.8%)**
31-40	**0**	**8**	**8 (10.8%)**
41-50	**1**	**12**	**13 (17.6%)**
51-60	**2**	**11**	**13 (17.6%)**
61-70	**2**	**11**	**13 (17.6%)**
71-80	**2**	**10**	**12 (16.2%)**
81-90	**1**	**4**	**5 (6.8%)**
Total	**9**	**65**	**74 (100%)**

Hospitalization for more than 21 days in ICU, use of urinary catheter, steroid drugs and broad-spectrum antibiotic as well as history of diabetes, hematologic malignancies, and COPD were some variables related to candiduria. The most common contributing factors were diabetes (48.6%), urinary catheter (16.2%) and use of steroid drugs and broad-spectrum antibiotics (14.8%) (Table 3).

Table 3- Predisposing factors in patients with candiduria

Underlying disease	Number (%)
Diabetes	36 (48.6%)
urinary catheter	12 (16.2%)
Use of steroid drugs and broad-spectrum antibiotics	11 (14.8%)
Hematologic malignancies	7 (9.4%)
Hospitalization for more than 21 days in the ICU	7 (9.4%)
COPD	1 (1.3%)
Total	74 (100%)

The frequency of candiduria was highest in patients from ICU (41.8%) and the internal medicine ward (31%). Based on the morphological characteristics of the colonies formed on the CHROMagar *Candida* medium, isolates including *C. albicans* complex (n=44; 59.4%), *C. glabrata* (n= 16; 21.6%), *C. tropicalis* (n= 10; 13.5%), *C. krusei* (n= 3; 4%) and other *Candida* spp. (n= 1; 1.3%) were identified (Table 4). Amplifications of the ITS region of the isolates resulted in a pattern of products ranging 500-800 bp. The PCR-RFLP method confirmed the result of morphological method (Figure 1). Accordingly, one isolate was identified as *C. parapsilosis* complex using intein-containing vacuolar ATPase precursor genes primers, but no *C. orthopsilosis*, and *C. metapsilosis* species were identified. Therefore, the isolate was identified as *C. parapsilosis* sensu stricto (data not shown). For *C. albicans* complex, a product of about 941 bp was yielded using the *HWP*1 primers, confirming presence of *C. albicans* sensu stricto species.

Table 4- The frequency of *Candida* spp. identified using CHROMagar *Candida* medium and molecular method

Colony color	CHROMagar Candida results	Molecular results	Number (%)
Light green-Green	*C. albicans* complex	*C. albicans*	44 (59.4%)
Purple or dark pink	*C. glabrata*	*C. glabrata*	16 (21.6%)
Metallic blue	*C. tropicalis*	*C. tropicalis*	10 (13.5%)
Pink, fuzzy	*C. krusei*	*C. krusei*	3 (4%)
white	Other *Candida* spp	*C. parapsilosis*	1 (1.3%)
			Total: 74

Figure 1. (A): Results of gel electrophoresis of PCR products of the ITS region. (B): Electrophoresis image of PCR-RFLP (ITS region digested with Msp1) products on 2% agarose gel [M: 100 bp DNA marker; 1, 3, 4: *C. krusei* (250, 260 bp); 2, 5, 6, 7: *C. albicans* complex (239, 298 bp)]. (C): Electrophoresis image of PCR-RFLP (ITS region digested with *Msp*1) on 2% agarose gel [M: 100 bp DNA marker; 1, 3, 4, 6, 7: *C. albicans* complex (239, 298 bp); 2: *C. glabrata* (320, 561bp) 5: *C. tropicalis* (186, 340bp); 8, 9, 10: *C. parapsilosis* (520 bp, no cutting site)]. (D): Electrophoresis image of PCR products by

HWP1 on 2% agarose gel [M: 100 bp DNA marker; 1-9: *C. albicans* (941bp)].

Figure 2 demonstrates the frequency of *Candida* spp. In different wards. The most common isolates in the ICU were *C. albicans* (n= 20; 64.5%), followed by *C. glabrata* (n= 6; 17.6%), *C. tropicalis* (n= 4; 12.9%), *C. krusei* (n= 1; 3.2%).

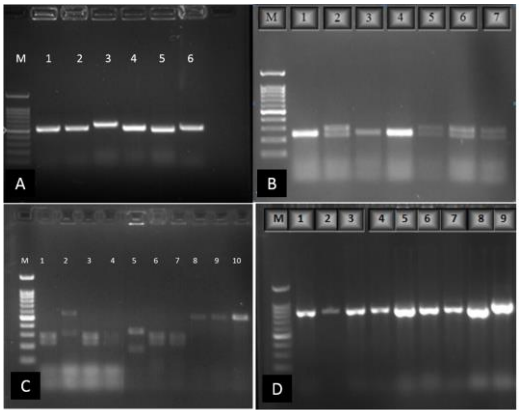

Figure 1- Results of gel electrophoresis of PCR products of the ITS region. (B): Electrophoresis image of PCR-RFLP (ITS region digested with Msp1) products on 2% agarose gel

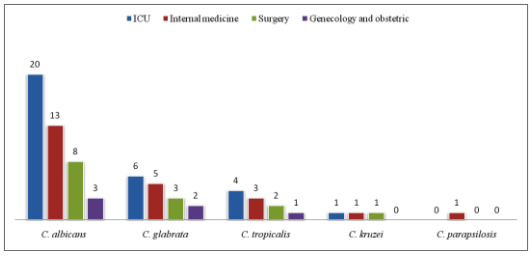

Figure 2-Frequency of *Candida* spp. in different hospital wards

DISCUSSION

Over the past decades, there has been a significant increase in the incidence of opportunistic urinary tract pathogens. Nowadays, candiduria in hospitalized patients, especially those admitted to ICU, is increasing rapidly (14-16). Accurate identification of *Candida* species isolated from urine specimens of hospitalized patients is essential for proper treatment management. In the present study, the frequency of candiduria was estimated at 14%. The prevalence of candiduria among hospitalized patients is estimated at 6.5-20% (24). According to several studies in Iran, the average prevalence of candiduria is around 16.5% (25). The highest and lowest frequency of candiduria in Iran were reported from Qazvin (32.3%) and Khuzestan (5.2%) provinces, respectively (26, 27). In our study, a high frequency of candiduria was seen in specimens taken from women (87.8%). Various studies have demonstrated that up to 30% of healthy women may have vaginal colonization of *Candida* species colonization in the species. Due to the anatomy of women, colonization of *Candida* spp. can spread to the bladder and kidneys, subsequently causing UTI (28-30). As expected, the frequency of candiduria was higher in older patients (41-70 years). Generally, older people are more exposed to candiduria due to natural changes in the immune system, prolonged hospitalization, and the use of urinary catheters (31, 32). Our results showed that diabetes (48.6%), followed by urinary catheters (16.2%) were the most common predisposing factors for candiduria. The prevalence of diabetes mellitus in candiduria patients is reported to be 39% (33). Patient with diabetics have a weakened immune system due to dysfunction of phagocytosis, which reduces the host's resistance to *Candida* spp. invasion (5, 34). In one study, prolonged use of urinary catheters increased the risk for candiduria by 12 folds (34). In our study, 14.8% of the patients with candiduria were using steroid drugs and broad-spectrum antibiotics. In a study by Guler and colleagues, the risk of developing candiduria in patients with a history of antibiotic use increased 6-fold (34). Various studies have shown that the use of antibiotics reduces phagocytic activity and antibody production, thereby negatively

affecting the host resistance against infection by *Candida* spp. (33, 35). In our study, hematologic malignancies (9.4%) were identified as another predisposing factor for candiduria in hospitalized patients. In a study by Guler et al., 7.8% of patients with candiduria had cancer, and malignancies increased the risk of candiduria by 0.2 fold (34). In the present study, the highest frequency of candiduria was highest among ICU patients (41.8%), which is in line with findings of a previous study (36). We found *C. albicans* (64.5%) followed by *C. glabrata* (17.6%) as the most commonly isolated pathogens from patients with candiduria. This result is consistent with findings of other studies in Iran (11, 37-39). In various studies, *C. albicans* and *C. glabrata* have been reported as the most frequent causes of candiduria with prevalence rate of 21-72% and 5-33%, respectively (34). However, in some studies, *C. glabrata* has been identified as the dominant species followed by *C. albicans* (40, 41). The inconsistency in the rate of *Candida* spp. could be associated with difference in the geographical areas and populations of studies (11). In recent years, non-albicans *Candida* has emerged in hospitalized patients, especially in those with chronic degenerative diseases or trauma (42-44). Appropriate identification and differentiation of the species in the *C. albicans* complex and *C. parapsilosis* complex is clinically important. Various studies have observed differences in the antifungal susceptibility patterns of these species. However, identification down to the species level using *HWP1* and intein-containing vacuolar ATPase precursor genes primer is necessary to establish appropriate antifungal therapy (23). The method used in our study is comparable to matrix-assisted laser desorption/ionization-time of flight platforms and other PCR-based methods from different aspects including, time required for each test and costs.

CONCLUSION

In our study, the frequency of candiduria was estimated at 14% among hospitalized patients. Based on the results, conventional and molecular methods produced similar results for identification of *Candida* species. However, accurate identification of *Candida* spp. Requires the use of molecular techniques such as PCR-RFLP, *HWP1*, and intein-containing vacuolar ATPase precursor genes. Nevertheless, chromogenic methods such as CHROMagar *Candida* can be used for diagnosis of *Candida* spp. in laboratories with limited resources.

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DECLARATIONS

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Ethics approvals and consent to participate

The study was approved by Ethics Committee of Islamic Azad University of Sari (ethical code: IR.IAU.SARI.REC.1399.051). Written informed consent was also taken from all participants.

Conflict of interest

The authors declare that there is no conflict of interest regarding publication of this article

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