

Phenotypic Evaluation of Strains of *Candida albicans* and Non-*albicans* Candida Species in Patients with Vulvovaginal Candidiasis Visiting Amir-Momenin Hospital in Zabol, Iran in 2019

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ABSTRACT

Background & Objective: Vulvovaginal candidiasis (VVC) is a common vaginal yeast infection in women. The present study aimed to determine the phenotype of *Candida albicans* and non-*albicans* Candida species in VVC cases.

Materials & Methods: This was a cross-sectional study on 65 patients suspected of VVC through a visit by a gynecologist. They were cultured on CHROMagar and Sabouraud dextrose agar (SDA). If morphology of the colonies could be detected through microscopic inspection, physiological tests were used to identify individual yeast species.

Results: Out of 65 colonies, 53.8% had negative cultures. The frequency of positive cultures for *Candida* were also calculated (*C. albicans* = 38.5%, *C. glabrata* = 6.15%, and *C. krusei* = 1.53%). Most of culture-negative cases had no history of antibiotic therapy (94.3%) while most of culture-positive cases had a history of fluconazole therapy (56% in *C. albicans* isolates and 40% in non-*C. albicans* isolates). Relapse rate was calculated as 29.2%. Of studied patients, 80% had no underlying disease, 15.4% had a history of diabetes, and 4.6% had a history of corticosteroid therapy. Less than half negative-culture cases had an undergraduate degree (45.7%).

Conclusion: The incidence of VVC depends on various factors including occupation, underlying disease and history of antibiotic therapy. The most common cause of VVC is *C. glabrata*, secondary to *C. albicans*. Relapse infection rates can be reduced by increasing knowledge on clinical data, underlying diseases, mechanism of the organism, cause of infection, and effective treatment.

Keywords: *Candida albicans*, Vulvovaginitis, Non-*albicans* Candida species



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Introduction

Candidiasis is a primary or secondary infection caused by *Candida* species. *Candida albicans* is the most common cause of the infection. The infection tends to run a clinical course of either acute, subacute, chronic or sporadic. The infection may be localized to the mouth, throat, skin, vagina, nails and other organs or become systemic as in septicemia, endocarditis, and meningitis. *C. albicans* is the most common causes of symptomatic and asymptomatic vulvovaginitis (1). It is currently one of the most important public health issues in both rural and urban areas in Iran. The statistics released in the UK in the recent decade suggested a dramatic increase in the incidence of VVC (2). Candidiasis is the second most common cause of vaginal infections in the US. Approximately 75% of all

women experience one episode of VVC at least once during their life. Roughly 40-50% of women may experience a second episode of VVC during the childbearing years whereas 5% of women report the recurrence of VVC (3). It is estimated that 10-20% of women develop acute complicated symptomatic VVC (2). *C. albicans* still remains the most common fungal agent isolated from clinical samples of the patients diagnosed with VVC given the following factors; a) candidiasis causes a wide range of infections, b) invasive and systemic infections has high lethal rate, c) the number of patients prone to various fungal diseases (e.g. candidiasis) is increasing, d) new molecular biological techniques are used to identify *Candida* species in VVC isolates (1). Numerous genetic,

biological and, behavioral factors contribute to colonization rate of *Candida* and relapse infection rate. These factors include antibiotic use, pregnancy, high-dose estrogen birth control pills, and uncontrolled diabetes mellitus (4). Candidiasis encompasses a wide variety of clinical syndromes caused by *Candida*. It may spread to different body parts including the skin, nails, mouth, digestive tract, respiratory tract, and genital tract (5). VVC is one of the most common fungal infections in women caused by abnormal growth of yeasts in the genital tract mucosa. It has increased dramatically in the recent years (6). Most VVC cases are caused by *C. albicans* (80 to 90%) as it adheres to vaginal epithelium more readily than other *Candida* species (7-9). *C. albicans* can be a member of normal oral, intestinal and vaginal flora without causing any overt disease. Any disturbance in normal balance of microbial flora leads to abnormal growth of *C. albicans* causing severe mucosal and cutaneous infections, VVC, oral thrush or other fungal diseases. Other *Candida* species (e.g. *C. glabrata* and *C. tropicalis*) that cause VVC are resistant to anti-fungal agents (9). The most important predisposing factors to VVC in women are immunosuppressants, immunodeficiency, uncontrolled diabetes mellitus, intrauterine devices, excessive sexual activity, pregnancy, tight and nylon underwear, antibacterial therapy and high-dose estrogen birth control pills (10,11). VVC is associated with various symptoms including itching, burning, pain during intercourse, vulvovaginal redness and inflammation, unusual and foul smelling vaginal discharge causing not only physical fatigue but also psychological disorders, especially in chronic recurrent cases due to persistence of the symptoms. It consequently diminishes quality of life (12). VVC is the second most common cause of vaginitis, secondary to bacterial vaginosis (13). Almost 75% of women experience at least one episode of VVC in their lifetime. Of these, nearly 50% experience two or more than two episodes of VVC each year while 5% of these experience four or more than four episodes of VVC called recurrent VVC (14).

Various studies have reported the prevalence of VVC as 5-75% in Iran. The prevalence of VVC was reported in different cities in Iran including 32.8% in Shahrekord (15), 46% in Qazvin (16), 9.1% in Kashan (17), 9.3% in Shiraz (18), 40.2% in Babol, and 50.8% in Tehran (19). Almost all patients are treated based on medical records and clinical symptoms. However, diagnosis of VVC based on medical records and clinical manifestation is not feasible since the symptoms are not specific to VVC. Microscopic inspection and vaginal pH measurement also do not help to diagnose VVC. Culture techniques can be used for accurate diagnosis of VVC (20).

Panahi *et al.* (2008) examined 240 patients complaining of itching, burning and abnormal vaginal discharge and isolated *Candida* species from 122 cases (50.8%) in southwest of Tehran (19). Paulitsch *et al.* examined 10463 patients suspected of VVC in Australia

in a five-year period (2000–2004) and 3184 (34.4%) samples showed positive cultures (21).

The most important pathogens responsible for candidiasis are *C. albicans*, *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. pseudotropicalis*, *C. parapsilosis*, *C. stellatoidea*, and *C. tropicalis*. *C. albicans* is the most common cause of candidiasis. It is a resident of normal gastrointestinal, oral mucosal and vaginal flora. It is often passed on to babies during the birth. Other *Candida* species are either members of normal cutaneous and mucosal flora or found in nature, soil and various materials. These non-albicans *Candida* species are less pathogenic and virulent than *C. albicans* (22, 23). Non-albicans *Candida* species were estimated to cause recurrent VVC in 15-47% of the cases. Some believe that widespread use of antifungal drugs has increased the incidence of non-albicans *Candida* infections. Although a three-day course of imidazole therapy may inhibit growth of *C. albicans*, it disrupts the natural balance in the vaginal flora that lead to an alarming rise in growth of non-albicans *Candida* species. Most non-albicans *Candida* species are resistant to antifungal agents. *C. glabrata* and *C. krusei* exhibited higher resistance to fluconazole than other species. Various methods are used for identification of *Candida* species including phenotypic, culture and genotypic techniques. Culture techniques is the most common identification method in Iran. It is not only time consuming but also has lower sensitivity for detection of *Candida* species (24, 25).

By taking into account the above-mentioned materials regarding precise identification of *Candida* species and its effective treatment, the present study aimed to identify *C. albicans* and non-albicans *Candida* species in VVC cases visiting Amir-Al-Momenin Hospital in Zabol, Iran, using phenotypic techniques.

Materials and Methods

This was a descriptive, analytical, cross-sectional study. Nonprobability sampling was used to select the samples from the patients suspected of VVC (representing such symptoms as itching, burning, redness, curd-like vaginal discharge) visiting the gynecology clinic of Amir Al Momenin Hospital in Zabol in a six-month period. Informed consent forms were collected from the patients who were diagnosed by a gynecologist. They were divided into various groups based on clinical symptoms. A questionnaire was designed to collect data on clinical manifestations, severity of disease (mild, moderate, and severe), demographic characteristics (e.g. age, gender, history of VVC, pregnancy, underlying diseases, antibiotic use, immunocompromised (corticosteroids), history of fluconazole therapy and other medications, relapse infection rate and hormone therapy). Vaginal specimens were prepared by a specialist and poured into sterile Falcon tubes containing 1 to 2 mL of sterile physiological saline. The patients were examined in the lithotomy position. A sterile speculum without lubricant was used to inspect the vagina and cervix for

clinical signs of vaginal inflammation and redness as well as shape, color, thickness and odor of vaginal discharge. Two sterile cotton swabs were inserted into the posterior fornix and cervix to take samples. The first swab was cultured on SDA using sterile tubes in the immediate vicinity of the alcoholic flame. The second swab was mixed with a drop of 10% KOH solution on a slide. The specimens were immediately transferred to the Mycological Laboratory for microscopic inspection. A milky white curd-like smooth fungal colony was visible after 24 to 48 hours that gradually grew to a folded colony. Pseudo-mycelium and true mycelium formations were visible in the cultures. Positive cultures were detected. *Candida*-positive cultures were grown on CHROMagar culture media to detect *Candida* species based on color of the colonies. The culture medium was kept in an incubator at 35°C and examined after 24 hours. *Candida* species form distinct mucoid colonies on SDA medium containing chloramphenicol (SC). Most *Candida* species grow rapidly except for *C. glabrata*, which requires longer period of incubation.

The tests used for *Candida* identifications were production of germ tubes and chlamydoconidia as well as pigmentation in CHROMagar media. Collected data were analyzed using Chi-square and t-test.

Results

Of studied cases, 65 were suspected of candidiasis. More than half of the cases (53.8%) showed negative cultures. Frequency of *Candida* species were 25 cases of *C. albicans* (38.5%), 3 cases of *C. glabrata* (4.6%), one case of *C. krusei* (1.5%) and one case of *C. parapsilosis* (1.5%).

Direct Microscopy and SDA Culture

The samples were prepared on a slide with 10% KOH for direct microscopic inspection. Some of vaginal swabs were cultured on SC and kept at 30°C for 24 to 48 hours for phenotypic evaluation. Of 65 samples, 30 slides were culture positive for *Candida* in direct microscopy.

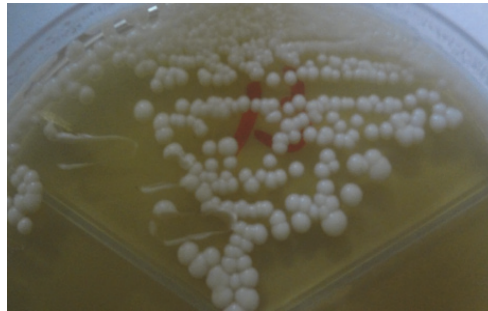


Figure 1. A slide of *Candida* isolates cultured on SDA

Results of CHROMagar Culture Medium

All 30 clinical isolates from SDA were grown on CHROMagar for phenotypic evaluation. *C. albicans* was also grown on the medium as control. *C. albicans* appeared as light green colonies (Figure 2c). The

colonies were identified based on their color 25 isolates (71.42%) produced light green colonies (*C. albicans* or *C. dubliniensis*), 3 isolates (10%) produced dark pink colonies (*C. glabrata*), 1 isolate (3.33%) produced pink fuzzy colonies (*C. krusei*), and 1 isolate (3.33%) produced pale pink colonies (*C. parapsilosis*) (Figure 2d).

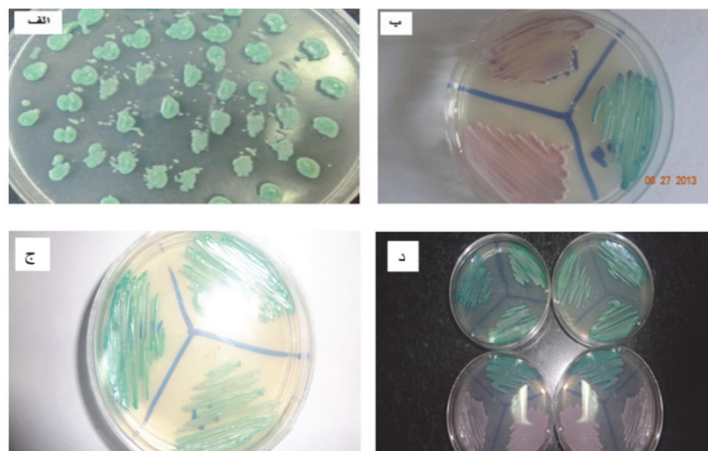


Figure 2. *Candida* Isolates grown on CHROMagar; A) *C. albicans* as control, B) *C. glabrata* as dark pink colonies, C) *C. albicans* or *C. dubliniensis* as light green colonies, D) *C. parapsilosis* as pale pink colonies

Culture on Corn Meal Agar with Tween 80 and Production of Germ Tube

The test was performed to study morphology of all specimens. *C. albicans* can produce chlamydospores at 25°C for 24 hours (Figure 3B). *C. krusei* was used as the negative control (Figure 3A). The results of culture on corn meal agar with tween 80 (a primary distinction

method of yeast species) showed that 25 isolates (71.42%) were able to produce chlamydospores at 25°C for 24 hours. These were identified as *C. albicans*. Germ-tube test with human serum on 65 isolates from S medium showed that 30 isolates were germ tube-positive and 35 isolates were germ tube-negative (ATCC10231 strain of *C. albicans* was used as control).

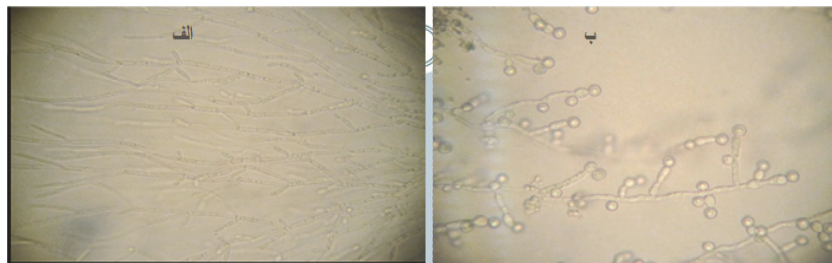


Figure 3. Sample of isolates on corn mill agar with tween 80; A) no production of chlamydospores in *C. krusei* colonies, B) production of chlamydospores in *C. albicans* colonies

Most infections were moderate (66.2%) followed by severe (18.5%) and mild (15.4%) infection. The severe cases were caused by *C. albicans* (64%), and moderate

cases were caused by non-albicans *Candida* species (60%) and negative cultures (68.6%). The difference was statistically significant ($P=0.001$).

Table 1. Severity of disease and cause of infection

Severity of disease		Mild	Moderate	Severe	Total
Cause of infection					
<i>Candida albicans</i>	Frequency	0	16	9	25
	Percent	0%	64%	36%	100%
Non-albicans <i>Candida</i>	Frequency	0	3	2	5
	Percent	0%	60%	40%	100%
Culture-negative	Frequency	10	24	1	35
	Percent	28.6%	68.6%	2.8%	100%
Total	Frequency	10	43	12	65
	Percent	15.4%	66.2%	18.4%	100%
P-value		0.001			

Nearly 70% (70.8%) of the cases had no history of antibiotic therapy, 24.6% had a history of fluconazole therapy, 3.1% had a history of azithromycin, and 1.5% had a history of azithromycin + metronidazole therapy. More than 90% (94.3%) of the cases with negative cultures had no history of antibiotic therapy whereas 56% of positive cultures for *C. albicans* and 40% positive cultures for non-albicans *Candida* had a history of fluconazole therapy. The difference was statistically significant ($P=0.000$), which indicated that

history of antibiotic therapy increased the number of positive cultures.

The relapse rate was 29.2% and non-relapse rate was 70.8%. Relapse rates in negative cultures and positive cultures (positive for both *C. albicans* and non-albicans *Candida*) were respectively as 2.9% and 60%. Non-relapse rate in negative cultures was 97.1%. The difference was statistically significant ($P=0.000$), which showed that relapse rate reduced in negative cultures.

Table 2. Relapse rate and cause of infection

Relapse rate		Yes	No	Total
Cause of infection				
<i>C. albicans</i>	Frequency	15	10	25
	Percent	60%	40%	100%
Non-albicans <i>Candida</i>	Frequency	3	2	5
	Percent	60%	40%	100%

Relapse rate Cause of infection		Yes	No	Total
Negative cultures	Frequency	1	34	35
	Percent	2.9%	97.1%	100%
Total	Frequency	19	46	65
	Percent	29.2%	70.8%	100%
P-value			0.000	

No underlying disease was reported in 80% of cases, while 15.4% had a history of diabetes, and 4.6% had a history of Corticosteroid therapy. No cases of immunodeficiency and cancer was reported. No underlying disease was reported in 97.1% of the cases with negative cultures; however, a history of diabetes (32%) and corticosteroid therapy (8%) were reported in positive cultures for *C. albicans*. A history of diabetes (20%) and corticosteroid use (20%) were reported in positive cultures for non-albicans *Candida*. The difference was statistically significant ($P=0.003$), which indicated that underlying diseases increased the number of positive cultures.

Most cases had less than a high school diploma (49.2%) and the rest had an academic degree (20%), a high school diploma (18.5%), and an elementary degree (9.2%). The least number of cases were illiterate (3.1%). The cases with less than a high school diploma were 45.7% in negative cultures, 56% in positive cultures for *C. albicans* and 40% in positive cultures for non-albicans *Candida*. The difference was not statistically significant ($P=0.703$). Therefore, education had no association with positive or negative cultures in VVC cases.

Most VVC cases were housewives (76.9%) and the rest were employees (12.3%), teachers (6.2%), and unemployed (4.6%). Most of negative cultures (88.6%) and positive cultures for *C. albicans* (68%) were housewives. The difference was statistically significant ($P=0.004$).

Discussion

The present study aimed to evaluate phenotype of *C. albicans* and non-albicans *Candida* species in VVC cases visiting Amir Al Momenin Hospital in Zabol, Iran, in 2019. This was the first study on VVC cases in Zabol. The results showed 53.8% negative cultures, 38.5% positive cultures for *C. albicans* and 7.7% positive cultures for non-albicans *Candida* species.

VVC is an opportunistic mucosal infection accounting for one-third of vaginitis cases. *Candida* species is a member of normal vaginal flora in 20-50% of women and 75% of women experience one episode of VVC in their lifetime while 45% develop the infection more than once in their lifetime (acute form). Recurrent candidiasis refers to four or more than four episodes of the infection within a year (26).

Fungal infections account for 35-40% of vaginitis cases (27). Varied prevalence of VVC is reported in

different countries including 17.4% in Turkey, 12.6% in Netherlands, and 39% in Iraq (27-29). The statistics released on VVC cases also varied in Iran including 33.8% in Sanandaj, 46.8% in Hamadan, 2.09% in Shahrekord, and 12.3% in Kashan (17, 30, 31).

Sixty-five colonies were assessed in the present study. Of these, 53.8% were negative cultures, 38.5% were positive for *C. albicans*, and 7.7% were positive for non-albicans *Candida*. The frequencies of other *Candida* species in studied colonies were 3 cases of *C. glabrata* (4.6%), one case of *C. krusei* (1.5%), and one case of *C. parapsilosis* (1.5%). Nezmata *et al.* found out that 40% of studied colonies were positive for *Candida*. Of these, 81% were caused by *C. albicans* and the rest were caused by non-albicans *Candida* (32). Sohrabi *et al.* studied 150 VVC cases including 87 positive cultures. Of these, 72 cases were caused by *C. albicans*, 12 cases by *C. glabrata*, and 2 cases by *C. tropicalis* (33). Flahati *et al.* (2008) studied 150 vaginitis cases and reported 80 VVC cases mostly caused by *C. albicans* and less caused by *C. krusei* and *C. guilliermondii* (34). Mahmoudabadi *et al.* studied 300 cases in Ahwaz in 2009. Of these, 49% had VVC including 43.8% cases of recurrent VVC and 51.7% cases of acute VVC. The most common cause of VVC was *C. albicans* followed by *C. glabrata*, and *C. dubliniensis* in this study (35). Kennedy *et al.* (2006) studied 100 isolates and reported the distribution of *Candida* as 86% *C. albicans*, 7% *C. glabrata*, 4% *Candida lusitanae*, 2% *C. parapsilosis* and 1% *C. tropicalis* (36). Paulitsch *et al.* reported 3184 (34.4%) positive cultures for *Candida* among 10463 cases in a five-year period (2000–2004) in Australia (21). Moreira *et al.* reported 63% positive cultures for *Candida* among the cases with clinical candidiasis (37). Of these, 46.2% were diagnosed with VVC in SDA culture medium. Many other studies estimated the prevalence of VVC as 15-30% (38). The prevalence of VVC was high (47.14%) in the present study. Therefore, treatment cannot be determined based on clinical symptoms and further assessments were needed. Pakshir isolated 43% VVC cases in 2007 (38). Aghamirian *et al.* identified 46% VVC cases grown on SDA culture media (16). This evidence suggests that clinical symptoms and laboratory results do not overlap in VVC cases.

The most common cause of VVC was reported as *C. glabrata*, secondary to *C. albicans* (11-43%) (39-41).

Of studied cases, 70.8% had no history of antibiotic therapy, 24.6% had a history of fluconazole therapy, 3.1% had a history of azithromycin therapy, and 1.5% had a history of azithromycin + metronidazole therapy.

No history of antibiotic therapy was reported in 94.3% of negative cultures whereas history of fluconazole therapy was reported in 56% positive cultures for *C. albicans* and 40% positive cultures for non-albicans *Candida*. The difference was statistically significant ($P=0.000$), which indicated that history of antibiotic therapy increased the number of positive cultures. Hosseini *et al.* found 22 (28.9%) positive cultures for candidiasis among 76 cases (27.6%) with a history of antibiotic therapy. Of these, 15 cases (19.7%) were caused by *C. albicans*, 5 (7%) cases by *C. glabrata*, and 2 (4%) cases by *C. parapsilosis*. Of these, 5 (1.3%) had used fluconazole and 27 (6.7%) had used metronidazole. There was a significant relationship between the incidence of VVC and history of antibiotic therapy in the former study (29). Bitew *et al.* (2018) found 22% positive cultures for *Candida* with a history of antifungal agents and fluconazole use and 7.6% positive cultures for *Candida* with a history of fluconazole therapy in Ethiopia. The difference was not statistically significant ($P>0.05$). These results were not consistent with the results of the present study (42). Increasing use of antifungal drugs alter both type and distribution pattern of colonized species in the host. Different prescription of antifungal drugs and antibiotics affects the mortality rate of fungal infections (39).

No history of underlying disease was reported in 80% of VVC cases while 15.4% had a history of diabetes and 4.6% had a history of corticosteroid use in the present study. No case of immunodeficiency and cancer was reported in this study. No history of any underlying disease was reported in 97.1% of negative cultures whereas of positive cultures for *C. albicans*, 32% had a history of diabetes and 8% a history of corticosteroid use. Twenty percent history of diabetes and 20% history of corticosteroid use were reported in positive cultures for non-albicans *Candida* in this study. The difference was statistically significant ($P=0.003$), which indicated that underlying diseases increased the number of positive cultures for *Candida* species, which might be due to a weakened immune system and low CD4 count (27). Hosseini *et al.* studied 146 (36.13%) cases with a history of underlying disease among 404 cases suspected of VVC. Of these, 95 (65.1%) were positive for VVC including 88 cases (60.2%) caused by *C. albicans*, 3 cases (2%) caused by *C. parapsilosis*, and 4 cases caused by *C. tropicalis* (2.7%). They also found 6 (83.3%) isolates of *C. albicans* and 10 (9.7%) isolates of *C. glabrata* among 103 cases with no underlying disease. There was a significant relationship between underlying diseases and incidence of VVC (29). These results were consistent with the results of the present study.

The results of the study also showed that 76.9% of VVC cases were housewives followed by 12.3% employees, 6.2% teachers, and 4.6 unemployed. Housewives encompassed 88.6% of negative cultures and 68% of the infections caused by *C. albicans*. The difference was statistically significant ($P=0.004$). Shokouhi *et al.* (2013) and Zang *et al.* (2018) found no significant relationship between occupation and VVC.

These results were not consistent with the results of the present study (33, 40).

C. glabrata was the most common causes of VVC in this study, secondary to *C. albicans*. The prevalence of *C. albicans* was higher in Zabol compared to other cities of Iran. Recurrent VVC and severe VVC were mostly caused by non-albicans *Candida* species in this study.

The incidence of VVC depends on various factors including occupation, underlying disease and antibiotic therapy. *C. glabrata* is the most common causes of VVC, secondary to *C. albicans*. Relapse infection rate can be reduced by increasing knowledge on underlying disease, clinical data and mechanism of the organism, cause of the infection, and effective treatment. A comprehensive phenotypic panel of unique *Candida* strains was identified in this study.

It is recommended to expand molecular analysis by taking advantage of PCR-RFLP as a reliable identification method in future studies. It is also recommended to identify polymorphism of other non-albicans species that are resistant to antibiotics to take advantage of this resistant species as the control group in future studies since ATCC strain was the only standard control used in this study. In addition, with assessing more variables in a longer period with simultaneous use of culture and PCR techniques, it will be possible to identify the major causes of VVC in future studies. We also suggest to use a larger sample size in future studies.

It is recommended to assess genotypes of recurrent VVC cases resistant to fluconazole in addition to phenotypic evaluation and MIC of these cases in order to isolate resistance genes. It is also suggested to compare morphology and gene expression patterns in *C. albicans*.

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Conflict of Interest

Authors declared no conflict of interests.

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