

Epidemiology and Risk Factors for Candiduria in Hospitalized Patients at Dr. Soetomo Hospital, Surabaya, Indonesia

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Abstract

Background: Candiduria can represent a variety of conditions, from sample contamination, kidney and collecting system infections, to life-threatening disseminated candidiasis. The prevalence of candiduria is significantly higher in hospitalized patients and may be associated with an increased mortality rate. Until now, most candiduria research has been done in developed countries, while the prevalence varies widely in different parts of the world.

Objective: This study aimed to determine the epidemiology and risk factors for candiduria in hospitalized patients at Dr. Soetomo Hospital Surabaya from January to December 2020.

Methods: This study is an observational analytic study with a cross-sectional design using medical record data and a total sample of 301 samples consisting of 185 candiduria patients and 116 non-candiduria patients.

Results: Among 185 candiduria patients, most patients were female (67.6%) and dominated by the age group 45–59 years (40.5%). *Candida albicans* was found most commonly (42.7%). No resistance of the studied *Candida* species to Amphotericin B was found. The prevalence of candiduria in hospitalized patients was 0.55%. Variables that had a significant relationship with candiduria were diabetes mellitus ($p=0.005$; $PR=1.309$; 95% $CI=1.089–1.575$), antibiotic use ($p=0.006$; $PR=1.4$; 95% $CI=1.174–1.670$), and the use of an Intraurethral Catheter (IUC) ($p=0.008$; $PR=1.292$; 95% $CI=1.074–1.554$). While old age, female gender, and corticosteroid therapy had no association with candiduria.

Conclusion: The prevalence of candiduria is 0.55%. Diabetes mellitus, antibiotic use, and the use of an Intraurethral Catheter (IUC) have a significant relationship with candiduria in hospitalized patients.

Keywords: Candiduria; *Candida* species; antifungal agents; prevalence; risk factors.

1. Introduction

Candida spp. is a fungus that most often causes opportunistic infections in humans. This fungus is generally part of the normal flora of the body and can be found on the skin, mucous membranes, intestinal

tract, genito-urinary tract, and vagina [1, 2]. *Candida* can cause an infection if it grows out of control or enters deep into the body, usually affecting someone with a compromised immune system [3].

An invasion of *Candida* spp. in the urinary tract can be identified by the finding of *Candida* spp. in urine or what can be called candiduria [4]. Candiduria may indicate a variety of conditions requiring interpretation, ranging from sample contamination, kidney and collecting system infections, to life-threatening disseminated candidiasis [5]. Candiduria can also be a causative agent of Urinary Tract Infection (UTI) [6]. The National Healthcare Safety Network (NHSN) receives reports of UTIs as the most frequent type of Healthcare-Associated Infection (HAI) [7]. HAIs can affect patient morbidity and mortality as well as the quality of hospital health services [8].

Candiduria was found in 0.11–0.75% of positive urine samples from outpatients but was much more prevalent in 3.49–10.63% of inpatient urine samples [6]. Although the possibility of candiduria causing candidemia occurs in only about 3–4% of cases, 10% of all candidemia cases are related to previous episodes of candiduria [9]. Research conducted in Intensive Care Units (ICU) also shows that candiduria can be associated with increased mortality rates ranging from 19% to 50% [9].

The results of a study conducted by Guler *et al.* in 2006 showed that patients with candiduria were most frequently isolated with *Candida albicans* (68.62%). This study also showed that catheter use, urinary tract abnormalities, broad-spectrum antibiotics use, abdominal surgery, diabetes mellitus, use of corticosteroids and immunosuppressant agents, and the presence of malignant disease are risk factors for candiduria [10].

Research conducted by Savitri *et al.* in 2013 showed differences in results with previous studies and stated that catheter use, old age (≥ 60 years old), use of antibiotics, female gender, corticosteroid therapy, hematological malignancies, and care in the ICU are not risk factors for candiduria, while other results are in line, namely that diabetes mellitus is a risk factor for candiduria (P value=0,001) [11].

Until now, research on the epidemiology and risk factors for candiduria has been uncommon and mostly done in developed countries, while the prevalence varies widely in different parts of the world. Based on the earlier explanations, it is necessary to conduct more research to determine the epidemiology and risk factors for candiduria, especially in developing countries. It is hoped that this research will be able to provide an overview and information regarding the epidemiology and risk factors for candiduria in hospitalized patients that can be used as a reference for the prevention and management of candiduria.

2. Method

This research is an observational analytic study with a cross-sectional design. The data was obtained from urine culture examination results from the Clinical Microbiology Unit and inpatients' medical records with candiduria at Dr. Soetomo Hospital Surabaya. It was carried out from January to December 2020.

The population in this study were all inpatients at Dr. Soetomo Hospital Surabaya from January to December 2020. Inpatients above the age of 19 who had a urine culture examination were eligible for the sample. Candiduria patients were included when the number of colony-forming units (CFU) was greater than or equal to 10^3 CFU/mL. Patients that had more than one positive sample were only included once. Information such as patient characteristics (gender and age), the species and resistance patterns of *Candida* that cause candiduria, and the presence of risk factors (old age, female gender, diabetes mellitus, corticosteroid therapy, antibiotic use, and use of Intraurethral Catheter (IUC)) were collected and recorded for all enrolled patients.

All data from the investigation were analyzed using the Statistical Package for Social Sciences (SPSS) software. The dependent and independent variables were compared using the Chi-square (χ^2) or Fisher's exact test. P values below 0.05 were considered statistically significant.

3. Results

Among 33,495 inpatients, 332 patients aged over 19 years had their urine culture examined at the Clinical Microbiology Unit and found 211 of them were candiduria patients and 121 were not candiduria (found bacterial growth, not *Candida* spp.), seen from the results of the first isolate urine culture. After going through the inclusion and exclusion process, the final sample size was 301 patients consisting of 185 candiduria patients and 116 non-candiduria patients.

According to the data acquired, the prevalence of candiduria in hospitalized patients aged more than 19 years based on the results of the first urine culture examination found *Candida* spp. $\geq 10^3$ CFU/mL at Dr. Soetomo Hospital Surabaya from January to December 2020 was 0.55%.

The characteristics of the study subjects are presented in Table 1. Out of 185 patients with candiduria, 125 (67.6%) were female. As for the most age group, namely the age group of 45–59 years (40.5%), followed by the age group of 60–74 years (30.8%).

Table 1. Characteristics of candiduria patients

	Category	Frequency, n (%)
Sex	Male	60 (32,4%)
	Female	125 (67,6%)
Age	20–34	20 (10,8%)
	35–44	22 (11,9%)
	45–59	75 (40,5%)
	60–74	57 (30,8%)
	≥ 75	11 (5,9%)

In our study, 9 different *Candida* species were detected in candiduria patients at Dr. Soetomo Hospital Surabaya. *Candida albicans* (42.7%; n=79) was the most frequent microorganism isolated, followed by *Candida tropicalis* (31.4%; n=58), *Candida glabrata* (10.8%; n=20), *Candida parapsilosis* (10.3%; n=19), *Candida rugosa* (2.2%; n=4), *Candida krusei* (1.1%; n=2), *Candida lipolytica* (0.5%; n=1), *Candida guilliermondii* (0.5%; n=1), and *Candida lusitanae* (0.5%; n=1) [Fig. 1].

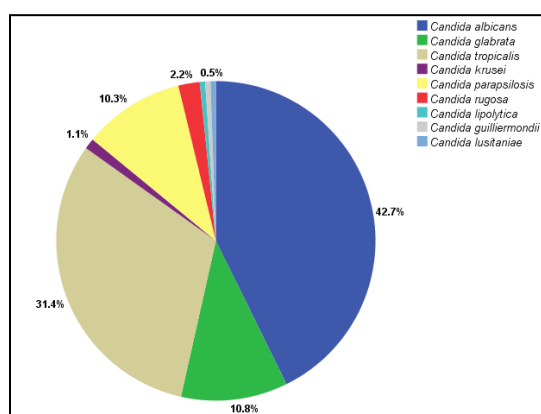


Fig. 1. Distribution of *Candida* species

The patterns of *Candida* resistance to several given antifungal agents are depicted in Table 2. There were no resistant isolates to Amphotericin B in this study. *Candida albicans* isolates showed resistance to fluconazole (2.6%), voriconazole (1.3%), and flucytosine (1.3%). Moreover, *Candida glabrata* showed resistance to caspofungin (21.1%), *Candida tropicalis* to fluconazole (1.7%), *Candida krusei* to flucytosine (100%), and *Candida guilliermondii* to caspofungin (100%).

Table 2. *Candida* resistance to antifungal agents

<i>Candida</i> species (n)	Antifungal agents (n)	Susceptible, n (%)	Intermediate, n (%)	Resistance, n (%)
<i>Candida albicans</i> (79)	Fluconazole (78)	76 (97.4%)	0	2 (2.6%)
	Voriconazole (77)	75 (97.4%)	1 (1.3%)	1 (1.3%)
	Micafungin (79)	79 (100%)	0	0
	Amphotericin B (77)	75 (97.4%)	2 (2.6%)	0
	Caspofungin (79)	79 (100%)	0	0
	Flucytosine (79)	78 (99.7%)	0	1 (1.3%)
<i>Candida glabrata</i> (20)	Voriconazole (20)	20 (100%)	0	0
	Micafungin (20)	20 (100%)	0	0
	Amphotericin B (20)	20 (100%)	0	0
	Caspofungin (19)	4 (21.1%)	11 (57.9%)	4 (21.1%)
	Flucytosine (19)	19 (100%)	0	0
<i>Candida tropicalis</i> (58)	Fluconazole (58)	57 (98.3%)	0	1 (1.7%)
	Voriconazole (58)	58 (100%)	0	0
	Micafungin (57)	57 (100%)	0	0
	Amphotericin B (58)	58 (100%)	0	0
	Caspofungin (55)	55 (100%)	0	0
	Flucytosine (58)	58 (100%)	0	0
<i>Candida krusei</i> (2)	Voriconazole (2)	2 (100%)	0	0
	Micafungin (2)	2 (100%)	0	0
	Amphotericin B (2)	2 (100%)	0	0
	Caspofungin (2)	1 (50%)	1 (50%)	0
	Flucytosine (2)	0	0	2 (100%)
<i>Candida parapsilosis</i> (19)	Fluconazole (19)	19 (100%)	0	0
	Voriconazole (19)	19 (100%)	0	0
	Micafungin (19)	19 (100%)	0	0
	Amphotericin B (19)	19 (100%)	0	0
	Caspofungin (19)	19 (100%)	0	0
	Flucytosine (19)	18 (94.7%)	1 (5.3%)	0
<i>Candida rugosa</i> (4)	Voriconazole (4)	4 (100%)	0	0
	Amphotericin B (4)	3 (75%)	1 (25%)	0
	Flucytosine (4)	4 (100%)	0	0
<i>Candida lipolytica</i> (1)	Voriconazole (1)	1 (100%)	0	0
	Amphotericin B (1)	1 (100%)	0	0
	Flucytosine (1)	0	1 (100%)	0
<i>Candida guilliermondii</i> (1)	Voriconazole (1)	0	1 (100%)	0
	Micafungin (1)	0	1 (100%)	0
	Amphotericin B (1)	1 (100%)	0	0
	Caspofungin (1)	0	0	1 (100%)
	Flucytosine (1)	1 (100%)	0	0
<i>Candida lusitanae</i> (1)	Voriconazole (1)	1 (100%)	0	0
	Amphotericin B (1)	1 (100%)	0	0
	Flucytosine (1)	1 (100%)	0	0

The statistical analysis of the possible risk factors for candiduria in hospitalized patients are shown in Table 3. Variables that had a significant relationship with candiduria were diabetes mellitus ($p=0.005$; PR=1.309; 95% CI=1.089–1.575), antibiotic use ($p=0.006$; PR=1.4; 95% CI=1.174–1.670), and the use of an

Intraurethral Catheter (IUC) ($p=0.008$; PR=1.292; 95% CI=1.074–1.554). Meanwhile, old age (≥ 60 years old), female gender, and corticosteroid therapy had no relationship with candiduria.

Table 3. Risk factors associated with candiduria in hospitalized patients

Variables	Candiduria				Total		PR (95% CI)	P value
	Positive		Negative					
	n	%	n	%	n	%		
Old age (≥60 years old)								
Yes	69	62.7	41	37.3	110	100	1.033 (0.859–1.241)	0.826
No	116	60.7	75	39.3	19	100		
Female								
Yes	125	64.1	70	35.9	195	100	1.132 (0.930–1.379)	0.249
No	60	56.6	46	43.4	106	100		
Diabetes mellitus								
Yes	107	69.5	47	30.5	154	100	1.309 (1.089–1.575)	0.005
No	78	53.1	69	46.9	147	100		
Corticosteroid therapy								
Yes	9	75	3	25	12	100	1.232 (0.877–1.729)	0.382
No	176	60.9	113	39.1	289	100		
Antibiotic use								
Yes	35	81.4	8	18.6	43	100	1.400 (1.174–1.670)	0.006
No	150	58.1	108	41.9	258	100		
Intraurethral Catheter (IUC)								
Yes	107	69	48	31	155	100	1.292 (1.074–1.554)	0.008
No	78	53.4	68	46.6	146	100		

4. Discussion

Over the decades, there has been an increase in opportunistic fungal infections of the urinary tract, the most common cause of which is *Candida* species [12]. *Candida* spp. in urine (candiduria) accounted for up to 10% of UTIs (Urinary Tract Infections) and has resulted in increased mortality over the last decades due to the use of new medical instruments, new treatments, surgeries, and also transplants [13].

Candiduria is rarely found in healthy individuals and is generally found in hospitalized patients [14]. In this study, the prevalence of candiduria in hospitalized patients aged more than 19 years based on the results of the first urine culture examination found *Candida* spp. $\geq 10^3$ CFU/mL at Dr. Soetomo Hospital Surabaya from January to December 2020 was 0.55%. Results from previous research conducted by He *et al.* in 2019 showed that 509 out of 31,648 (1.61%) inpatients were diagnosed with candiduria [15]. Candiduria was found in 0.11–0.75% of positive urine samples from outpatients but was much more prevalent in 3.49–10.63% of inpatient urine samples [6]. The results of this study have significant differences from the research conducted by Zarei-Mahmoudabadi *et al.* (2012) which stated that the prevalence of candiduria in hospitalized patients

was 16.5% [13]. This difference may usually be influenced by several conditions, such as geography, the type of hospital, and the sample studied [11].

In our study, candiduria was more prevalent in females compared to males. As in many previous studies, female patients predominate over male patients [10, 16]. Naturally, the prevalence of candiduria is more common in female patients compared to male patients due to the reasons of anatomical and functional characteristics of the urinary system [4]. It is probably due to the shorter length of the female urethra, transmission from the female genital tract to the urinary tract, and the anti-*Candida* activity of prostatic fluid in males [17]. Furthermore, because the female urethra's external opening is close to the vagina and anus, which have higher levels of bacteria and yeast (i.e., approximately 75% of women will experience at least one episode of vulvovaginal candidiasis) [18], bacteria and yeast can easily enter the vagina and then enter the bladder [19].

Candiduria occurrence rates differ by age group. This study showed that the highest distribution of candiduria patients in the age group was in the 45–59 year age group with 75 patients (40.5%), followed by the 60–74 year age group with 57 patients (30.8%). Two different studies showed that most cases of candiduria occurred in patients in the age group of 60-years and over [15, 20]. Research conducted in Iraq found that *Candida* infections of the urinary tract were more common in the 21–29 year age group with a proportion of 27.6%, whereas the 60-year and older age group had just 6.9% [16]. Similar to that research, a study conducted by Salehi *et al.* in 2016 also showed that the age group of 21–30 years were the most dominant [21]. The different variances in the candiduria age group may be influenced by various predisposing factors that can occur in each age group.

The most common *Candida* species found in this current study was *Candida albicans* (42.7%), followed by *Candida tropicalis* (31.4%) and *Candida glabrata* (10.8%). Similar results were also found in a study conducted by Salehi *et al.* in 2016, where *C. albicans* was the most common species (77.4%), followed by *C. tropicalis* (12.8%) and *C. glabrata* (5.46%) [21]. Moreover, several previous studies have consistently shown that *Candida albicans* was the most common species isolated from candiduria patients [6, 10, 13, 16]. According to Al-Mussawi and Al-Hussani (2019), this is because *C. albicans* has a high ability to attach to epithelial cells and its ability to produce true hyphae or germ tubes in infected tissues and high production of protein digestion enzymes and phospholipase enzymes [16].

Although *Candida albicans* was the most isolated species in this study, the prevalence of NACS (*Non-albicans Candida* spp.) in candiduria cannot be ignored, especially *C. tropicalis* and *C. glabrata*, which were the most common causes after *C. albicans*. *Non-albicans Candida* spp. (NACS) accounted for 62% of candiduria patient isolates in a study conducted by Abishek *et al.* in 2019 [22]. Several studies have also shown that *Candida tropicalis* [23] and *Candida glabrata* [24] identified as the most isolated urinary tract *Candida* species, with a percentage of 37.6% and 50%, respectively, higher than *C. albicans*. This incident may have occurred because NACS is more adaptable to the urinary system and more resistant to azoles compared to *C. albicans* [24].

A study conducted by Yashavanth *et al.* (2013) stated that *Candida albicans* was more susceptible to azoles when compared to NACS (*Non-albicans Candida* spp.) [20]. In a recent study, one isolate (1.7%) of *Candida tropicalis*, which belongs to the NACS, showed resistance to fluconazole. Fluconazole, itraconazole, and voriconazole were proven to be effective in inhibiting *Candida albicans* growth [25]. However, other results in this study showed that several *Candida albicans* isolates were also resistant to fluconazole (2.6%) and voriconazole (1.3%). Another research had a similar finding, with 55.2% of *C. albicans* isolates resistant to fluconazole [26].

In the *Candida glabrata* isolates studied, 21.1% of isolates were resistant to caspofungin, followed by 57.9% of isolates that were intermediate and 21.1% of susceptible isolates. Similar to the results of this study, other reports have also shown a failure of the antifungal caspofungin when treating *Candida glabrata* in the

incidence of candiduria [27]. Unlike caspofungin, the antifungal agent micafungin has been reported to be effective in the management of candiduria patients with *Candida glabrata* or *Candida albicans*, which are resistant to azoles [28]. Our study also showed that the antifungal micafungin was 100% susceptible to the tested *Candida* isolates. Despite its low urine concentration, micafungin is rapidly and well distributed to kidney and bladder tissues, which could explain its efficacy [29].

In this study, there was no resistance among the *Candida* species studied to amphotericin B. Amphotericin B is considered the gold standard in the treatment of candiduria. Despite having a broad spectrum and a low rate of resistance, nephrotoxicity and other severe side effects at varying doses limit the use of amphotericin B [30].

Other findings in this study showed that two isolates of *Candida krusei* were 100% resistant to the antifungal agent flucytosine. Flucytosine shows good activity against most *Candida* species and is excreted as an active drug in the urine. However, *C. krusei* is not susceptible to this antifungal agent [31].

The relationship between candiduria and several different possible risk factor variables was assessed in this study. According to several reports, old age is a risk factor for candiduria and its prevalence increases with age [32]. Episodes of candiduria in old age are typically associated with patient frailty and vulnerability [33]. However, there was no significant difference between old age and candiduria in our current study. This result is in line with previous research conducted by Kobayashi *et al.* in 2004, which showed no significant relationship between old age and the incidence of candiduria. Subjects in the study had an average age of 48.7 ± 19.8 years [34]. Furthermore, Bizuayehu *et al.* (2022) discovered that age had no significant difference between candiduria and non-candiduria patients (P value=0.92). The lack of association of candiduria with age may be explained by the predominance of the age group of the patients studied [35].

Female gender is another factor that may influence the occurrence of candiduria. The results of the statistical analysis in this study showed that there was no relationship between the female gender and the incidence of candiduria. A study conducted in Ethiopia found the same results, which stated that the female gender and the incidence of candiduria did not have a statistically significant relationship with a P value of 0.05 [35]. Theoretically, this might be due to the formation of estrogen-dependent mucous membranes in the bladder, which have an antimicrobial effect [11].

In this study, *Candida* growth in urine was broadly associated with diabetes mellitus. The result of this study was supported by the research of Zarei-Mahmoudabadi *et al.* (2012), which stated that diabetes mellitus is related to the growth of *Candida* in the urine (candiduria) [13]. Research conducted by Padawer *et al.* (2015) specifically stated that diabetes mellitus was statistically associated with the occurrence of candiduria colonized by *Candida albicans* [36]. In addition to those studies, a study conducted in Turkey in 2006 also showed that the risk of candiduria was increased by two folds in patients who had a history of diabetes mellitus compared to patients who did not have diabetes mellitus (P value=0.044; OR=2.002; 95% CI=1.013–3.957) [10]. Diabetic patients experience an increased threat of candiduria because they have a tendency for *Candida* colonization/infection through increased fungal growth in the urinary tract as a consequence of impaired phagocytic activity as a result of decreased host resistance to fungal invasion [17].

Corticosteroids are drugs that have been extensively used in almost all areas of medicine. Several studies have stated that corticosteroid therapy is associated with an increased incidence of candiduria [10, 17]. Research conducted by Ghiasian *et al.* (2014) stated that corticosteroid therapy was the third most common risk factor after antibiotics use and urinary catheterization [17]. The desired immunosuppressive and anti-inflammatory effects of corticosteroids can predispose patients to infection [37]. In particular, patients taking corticosteroids are vulnerable to invasive fungal and viral infections [38]. However, corticosteroids did not show a significant relationship with candiduria in our study. This condition may have occurred because most of the patients studied did not receive corticosteroid therapy during their hospitalization. Similar results were

obtained in research conducted at Dr. Kariadi Hospital Semarang in 2013, which stated that corticosteroid therapy was not a risk factor for candiduria (P value=1; OR=1; 95% CI=0.6–1.6) [11].

Many studies have stated that the use of antibiotics has a significant correlation with the occurrence of candiduria in hospitalized patients [13, 34, 39]. The same results were also obtained in our study. In addition, research conducted in Turkey in 2006 using a case-control design stated that the risk of candiduria would increase by 6 times in patients using antibiotics (P value=0.000; OR=6.00; 95% CI=2.42–2.89) [10]. The use of antibiotics can cause *Candida* colonization by suppressing endogenous bacterial flora. When the endogenous bacterial flora lysis due to the bacteriocidal effect of antibiotics, *Candida* species will grow more and more because of reduced competitors. This situation will make it easier for *Candida* spp. to reproduce by forming colonization. This colonization disrupts the function of phagocytosis, which can interfere with the body's defense system against *Candida* infections [11].

The last variable studied was the use of *Intraurethral Catheter* (IUC). In this current study, the use of Intraurethral Catheter (IUC) has a significant relationship with candiduria. This result is in line with previous studies [13, 15, 34]. In addition, a study with a case-control design stated that the risk of candiduria would increase 12 times in patients using an Intraurethral Catheter (IUC) (P value=0.000; OR=12.408; 95% CI=5.674–27.136) [10]. Biofilm formation on catheters and host-pathogen interactions are likely to be important factors contributing to the pathogenesis of candiduria in this condition [40].

One of the limitations of this study was that it couldn't specifically determine whether the candiduria patients studied were involved in the contamination of urine samples, colonization of the bladder and/or catheter, or infection of the upper or lower urinary tract due to incomplete data regarding patient symptoms.

5. Conclusion

This study documented that the prevalence of candiduria in hospitalized patients was 0.55% and varied according to the gender and age of the isolated patients. *Candida albicans* was the most common *Candida* species discovered. The findings of this study on the pattern of *Candida* resistance revealed that none of the *Candida* species investigated were resistant to the antifungal Amphotericin B. In addition, there was a strong correlation between diabetes mellitus, antibiotic use, and the use of an Intraurethral Catheter (IUC) with the occurrence of candiduria in hospitalized patients.

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