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Antifungal susceptibility patterns of *Candida* species colonizing the oral cavity of cancer patients attending two tertiary hospitals in southwest Nigeria

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Abstract:

Background: *Candida* species inhabit humans as commensals but become opportunistic pathogens in immunocompromised individuals. This yeast has developed resistance to anti-fungal medications and infection caused by it is associated with increased morbidity and mortality. Information on the yeast colonization profile and the antifungal sensitivity pattern in the Nigerian population is sparse. This study determined the prevalence and antifungal susceptibility patterns of oral *Candida* species among cancer patients attending two tertiary care hospitals in Osun State, southwest Nigeria.
Methodology: This was a case-control study of 165 cancer patients attending the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) Ile-Ife and Osun State University Teaching Hospital (OSUTH) Osogbo, and 165 age and sex matched apparently healthy controls recruited from Ife and Modakeke communities in Osun State, southwest Nigeria. Socio-demographic and clinical information were collected from each participant to determine potential risk factors for *Candida* colonization and resistance. Oral rinse samples were collected from each cancer patient and the healthy control. *Candida* species were isolated on Hicrome chromogenic agar and identified by characteristic yeast-like colonies and Gram-staining reaction. Antifungal susceptibility of the *Candida* species against six selected antifungal agents was determined by the disc diffusion method. Data were analyzed using Chi-square and Fisher Exact tests, with $p<0.05$ considered as statistical significance.
Results: *Candida* species were significantly more prevalent in oral cavity of the cancer patients (38.8%, n=64) than the controls (26.7%, n=44) ($p=0.0258$)**.** The prevalence was highest among elderly cancer patients above 70 years of age (58.3%, n=7), higher in females (42.3%, n=44) than males (32.8%, n=20) and higher among cancer patients on anti-cancer therapy (40.7%, n=50) than those who had not received therapy (33.3%, n=13). *Candida* species identified include *Candida albicans* (55.1%, n=70)*, Candida krusei/Pichia kudriavzevii* (27.6%, n=35)*, Candida parapsilosis* (11.8%, n=13), *Candida tropicalis* (3.1%, n=4), *Candida/Diutina rugosa* (1.6%, n=2) and *Candida/Nakaseomyces glabrata* (0.8%, n=1). The highest and lowest susceptibilities of the *Candida* species were to nystatin (95.2%, n=118) and fluconazole (42.7%, n=53) respectively. The frequency of multi-drug resistance (MDR) was significantly higher ($p<0.01$) among non-*albicans Candida* species (43.6%, n=24) than *C. albicans* (31.9%, n=22).
Conclusion: It was generally observed that *Candida* species were more prevalent in cancer patients than apparently healthy persons. The observed high resistance rates to commonly used azoles underscore the concerns about current empirical treatment options. Nystatin was the most effective drug against *Candida* species in the study population. Regular surveillance of anti-fungal susceptibility and anti-fungal stewardship aew urgently needed to mitigate resistance and improve patients outcomes.

Keywords: Oral colonization; *Candida*; anti-fungal; resistance; immunocompromised; cancer

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Profils de sensibilité aux antifongiques des espèces de *Candida* colonisant la cavité buccale de patients atteints de cancer, hospitalisés dans deux hôpitaux tertiaires du sud-ouest du Nigéria

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Résumé:

Contexte: Les espèces de *Candida* vivent chez l'homme commensales, mais deviennent des pathogènes opportunistes chez les personnes immunodéprimées. Cette levure a développé une résistance aux antifongiques et les infections qu'elle provoque sont associées à une augmentation de la morbidité et de la mortalité. Les informations sur le profil de colonisation des levures et le profil de sensibilité aux antifongiques au sein de la population nigériane sont rares. Cette étude a déterminé la prévalence et les profils de sensibilité aux antifongiques des espèces de *Candida* buccales chez des patients atteints de cancer fréquentant deux hôpitaux de soins tertiaires de l'État d'Osun, au sud-ouest du Nigéria.
Méthodologie: Il s'agissait d'une étude cas-témoins portant sur 165 patients atteints de cancer fréquentant le Complexe hospitalier universitaire Obafemi Awolowo (OAUTHC) d'Ile-Ife et l'Hôpital universitaire d'État d'Osun (OSUTH) d'Osogbo, et 165 témoins apparemment sains, appariés selon l'âge et le sexe, recrutés dans les communautés d'Ife et de Modakeke, dans l'État d'Osun, au sud-ouest du Nigéria. Des informations socio-démographiques et cliniques ont été recueillies auprès de chaque participant afin de déterminer les facteurs de risque potentiels de colonisation et de résistance à *Candida*. Des échantillons de bain de bouche ont été prélevés chez chaque patient atteint de cancer et chez le témoin sain. Les espèces de Candida ont été isolées sur gélose chromogène Hicrome et identifiées par des colonies caractéristiques de type levure et une réaction de coloration de Gram. La sensibilité antifongique des espèces de *Candida* à six agents antifongiques sélectionnés a été déterminée par la méthode de diffusion sur disque. Les données ont été analysées à l'aide des tests du Chi carré et de Fisher Exact, avec une valeur de $p<0,05$ considérée comme statistiquement significative.
Résultats: Les espèces de *Candida* étaient significativement plus prévalentes dans la cavité buccale des patients atteints de cancer (38,8%, n=64) que chez les témoins (26,7%, n=44) ($p=0,0258$). La prévalence était la plus élevée chez les patients atteints de cancer âgés de plus de 70 ans (58,3%, n=7), plus élevée chez les femmes (42,3%, n=44) que chez les hommes (32,8%, n=20) et plus élevée chez les patients atteints de cancer sous traitement anticancéreux (40,7%, n=50) que chez ceux n'en ayant pas reçu (33,3%, n=13). Français Les espèces de *Candida* identifiées comprennent *Candida albicans* (55,1%, n=70), *Candida krusei*/*Pichia kudriavzevii* (27,6%, n=35), *Candida parapsilosis* (11,8%, n=13), *Candida tropicalis* (3,1%, n=4), *Candida*/*Diutina rugosa* (1,6%, n=2) et *Candida*/*Nakaseomyces glabrata* (0,8%, n=1). Les sensibilités les plus élevées et les plus faibles des espèces de *Candida* étaient respectivement à la nystatine (95,2%, n=118) et au fluconazole (42,7%, n=53). La fréquence de la multirésistance aux médicaments (MDR) était significativement plus élevée ($p=0,01$) parmi les espèces de *Candida* non *albicans* (43,6%, n=24) que chez *C. albicans* (31,9%, n=22).
Conclusion: Il a été généralement observé que les espèces de *Candida* étaient plus répandues chez les patients atteints de cancer que chez les personnes apparemment en bonne santé. Les taux élevés de résistance observés aux azolés couramment utilisés soulignent les inquiétudes quant aux options thérapeutiques empiriques actuelles. La nystatine s'est avérée le médicament le plus efficace contre les espèces de *Candida* dans la population étudiée. Une surveillance régulière de la sensibilité aux antifongiques et une gestion responsable des antifongiques sont nécessaires de toute urgence pour atténuer la résistance et améliorer l'état de santé des patients.

Mots-clés: Colonisation buccale; *Candida*; antifongique; résistance; immunodépression; cancer

Introduction:

Candida albicans belong to the kingdom fungi, phylum Ascomycota, class Saccharomycetes, order Saccharomycetales and the family Saccharomycetaceae (1). This yeast that was in the past considered harmless is now known to be primarily responsible for

morbidity and mortality from fungal infections in immunocompromised and debilitated individuals, including cancer patients (2). It is a paradox that medical advancement over past few decades has led to a significant escalation in the incidence of life-threatening invasive fungal infections. However, the extent of the problem is under-reported due to challenges faced in diagnosing fungal infection. It is worrying to know that the mortality estimates due to fungal diseases could be five times higher than what is reported (3). Oladele and Denning (4) estimated that more than 11.8% of Nigerian population yearly suffer from serious fungal infection which is associated with substantial mortality. Among human fungal diseases, candidiasis caused by *Candida* species is the commonest and it is increasingly being reported in recent years (1,4).

However, a decline in the host immunity contributes to the development of candidiasis since *Candida* species exist as commensals in the host's skin as well as the gastrointestinal and genitourinary systems (5,6). Thus, they act as opportunistic pathogens which contribute to high morbidity and mortality from fungal infections among the immunocompromised (7). Factors that compromise the immune system includes low birth weight, cancer, diabetes, HIV/AIDS, burns, chemotherapy and organ transplantation. As a result of the immunocompromised state and the effect of chemotherapy in cancer patients, they are prone to fungal infections, majorly candidiasis, caused by *Candida* species (8).

Globally, after bacterial infection caused by *Clostridioides difficile, Neisseria gonorrhoeae* and Enterobacteriaceae, candidiasis now ranks as third to fourth most occurring nosocomial infections (9). Asymptomatic oral colonization often progresses to oropharyngeal candidiasis, characterized clinically by white pseudomembranous plaques (oral thrush) or erythematous ulcerations. In vulnerable patients, *Candida* species can cause systemic infections including candidaemia and disseminated candidiasis affecting multiple organs such as the heart valves, eyes, central nervous system, spleen, liver and bones. These invasive forms are associated with high morbidity and mortality, especially in immunocompromised hosts (10,11).

Fewer classes of antifungal drug compared with antibacterial drugs are available for the treatment of fungal infections, thus, limiting therapeutic options. A major factor that limits the scope of antifungal drug discovery and development is the fact that evolutionarily, when compared with other pathogens, fungi are the closest to man (12). Several classes of antifungal drugs which have been developed to treat infections caused by *Candida* species include the nucleoside analogs, allylamines (e.g. terbinafine), the azoles (e.g. fluconazole, itraconazole and voriconazole), echinocandins (e.g. caspofungin) and polyenes (amphotericin B and nystatin). However, *Candida* species have developed resistance to practically most of these drugs.

Almost all surveys on *Candida* colonization and infections in cancer patients come from the USA, Europe, and other developed countries (13,14). To date, there is lack of published report on oral *Candida* colonization and antifungal susceptibilities among cancer patients in Nigeria. Therefore, this study was aimed at determining the prevalence, species distribution and antifungal susceptibility of *Candida* species in cancer patients receiving treatment at two southwest Nigerian tertiary hospitals, in comparison to matched apparently healthy controls from the same geographical area.

Materials and method:

Study area and design:

This was a case-control study involving a total of 165 cancer patients receiving treatment at two tertiary hospitals in Osun State, Nigeria; Obafemi Awolowo University Teaching Hospital (OAUTHC) Ile-Ife and Osun State University Teaching Hospital (OSUTH), Osogbo, and 165 apparently healthy individuals, matched for sex and age, recruited from Ife and Modakeke communities in Osun State, Nigeria, as controls.

Processing of samples was carried out at the Department of Medical Microbiology and Parasitology, Faculty of Basic Medical Sciences, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria as well as the Department of Drugs Research and Production Unit, Faculty of Pharmacy at the same institution.

Ethical clearance:

Ethical clearance for this study was obtained from the Ethics and Research Committee of OAUTHC with national number; NHREC/27/02/2009a and international number approval number: IRB/IEC/0004553. Additional ethical clearance was obtained from the Ethics and Research Committee of OSUTH with protocol number: UTH/EC/2021/09/537.

Informed consent and data Collection:

Both written and verbal informed consents were obtained from all participants prior to enrolment. Structured questionnaires were administered to all the participants by the researchers to collect socio-demographic and clinical data. The information obtained from cancer patients include hospital number, age, sex, marital status, educational background, occupation, types of cancer, type of cancer therapy, duration of treatment, mouth

symptoms and the hospital ward.

Similar socio-demographic data excluding those that had to do with hospitalization were also obtained from the controls. All data were analysed anonymously throughout the study and confidentially kept. Occupation of participants were grouped based on the modified International Standard Classification of Occupation (ISCO-08) by the International Labour Organization.

Sample collection:

Samples were collected by using concentrated oral rinse technique in which 10ml of sterile distilled water was given in Universal bottles to cancer patients and the healthy controls recruited in this study to rinse their mouths (15). All the samples collection from cancer patients was carried out between June and November 2021 while collection from healthy controls was done between December 2021 and January 2023.

Isolation of *Candida* species from oral rinse:

Hicrome agar (Himedia, India) was prepared according to the manufacturer's specification. Oral rinse sample was cultured on Hicrome agar plates and incubated at 37°C for 48 hours after which the culture plates were observed for growth. Isolates with yeast-like colonies were selected for further studies. Gram-stained cells were observed under a light microscope.

Identification of *Candida* species

Candida species were identified on Hi-chrome agar, a chromogenic agar, based on their colonial colours. A dark green yeast colony which appeared different from *C. albicans* was molecularly identified. Each of the different coloured colonies was selected, sub-cultured on Sabouraud Dextrose Agar (SDA) and incubated at 37^{o}C for 18-24 hours for purity. The pure isolates were stored on SDA slants in cryovials and refrigerated at 4^{o}C for further studies.

Antifungal susceptibility testing

Antifungal susceptibility of the *Candida* isolates was determined against six antifungal agents (Liofilchem, Italy) which included fluconazole (100µg), itraconazole (50µg), voriconazole (1µg), amphotericin B (10µg), caspofungin (5µg) and nystatin (100IU) by the disc diffusion method in line with the Clinical and Laboratory Standards Institute (CLSI) document M44A2 (16). Zones of inhibition were measured and interpreted as susceptible (S), susceptible-dose dependent (SDD) or intermediate, and resistant (R) according to the CLSI guideline.

Data analysis:

Data were analysed using the R Core Team (2022) and the Jamovi project (2023) analysis software (17,18). The data analysis method used was Pearson's Chi-squared test while $p \leq 0.05$ was taken to be statistically significant.

Results:

Demographic characteristics of study participants:

The age of the cancer patients ranged from 7-87 years with a mean of 46.58±17.35 years while that of the controls ranged from 7 -95 years with a mean of 46.51±17.72 years (Table 1). Among the cancer patients, the most frequently occurring cancer type was leukaemia (41.2%, n=68), followed by breast cancer (30.9%, n=51). All the cancer types were grouped into two classes, solid tumour (50.9%, n=84) and haematological malignancies (49.1%, n=81) (Table 2).

Prevalence of *Candida* species in cancer patients:

The prevalence of *Candida* species in the oral cavity of the cancer patients (38.8%, n=64) was significantly higher (p=0.0258) than the healthy controls (26.7%, n=44) (Table 3). The association of demographic characteristics with prevalence of *Candida* species in cancer patients is shown in Table 4. The prevalence of *Candida* species was higher (though not statistically significant) in cancer patients who had started cancer therapy (40.7%, n=50) than those who were yet to start therapy (33.3%, n=13) (p=0.414).

Candida species isolated from cancer patients include *Candida albicans, Candida krusei/Pichia kudriavzevii, Candida parapsilosis*, *Candida tropicalis*, *Candida rugosa* and *Candida/Nakaseomyces glabrata* (Table 5). Similar species except *C. rugosa* and *C/N. glabrata* were isolated from the controls. Most of the Hicrome agar plates yielded single *Candida* species (84.3%, n=91) while a few had multiple *Candida* species (15.7%, n=17) (Table 6).

Table 1: Socio-demographic characteristics of case and control participants

Characteristics	Cases (%) (n=165)	Controls (%) (n=165)	Total (%) (n=330)	*p* value
Age group (years)				
≤10	8 (4.8)	8 (4.8)	16 (4.8)	1.000
11-20	7 (4.2)	7 (4.2)	14 (4.2)	
21-30	12 (7.3)	12 (7.3)	24 (7.3)	
31-40	25 (15.2)	25 (15.2)	50 (15.2)	
41-50	45 (27.3)	45 (27.3)	90 (27.3)	
51-60	35 (21.2)	35 (21.2)	70 (21.2)	
61-70	21 (12.7)	21 (12.7)	42 (12.7)	
>70	12 (7.3)	12 (7.3)	24 (7.3)	
Gender				
Female	104 (63.0)	104 (63.0)	208 (63.0)	1.000
Male	61 (37.0)	61 (37.0)	122 (37.0)	
Marital status				
Divorced/Separated	1 (0.6)	3 (1.8)	4 (1.2)	0.197
Married	116 (70.3)	121 (74.2)	237 (72.3)	
Single	29 (17.6)	30 (18.4)	59 (18.0)	
Widowed	19 (11.5)	9 (5.5)	28 (8.5)	
Level of Education				
No formal education	7 (4.3)	7 (4.3)	14 (4.3)	0.113
Primary	23 (14.0)	21 (12.8)	44 (13.4)	
Secondary	53 (32.3)	35 (21.3)	88 (26.8)	
Tertiary	81 (49.4)	101 (61.6)	182 (55.5)	
Occupation				
Agriculture	5 (3.0)	9 (5.8)	14 (4.4)	0.047
Clerical	2 (1.2)	1 (0.6)	3 (0.9)	
Crafts	8 (4.8)	4 (2.6)	12 (3.8)	
Machine	5 (3.0)	6 (3.9)	11 (3.4)	
Unemployed	11 (6.7)	4 (2.6)	15 (4.7)	
Professional	41 (24.8)	63 (40.6)	104 (32.5)	
Retiree	16 (9.7)	9 (5.8)	25 (7.8)	
Service and Trade	59 (35.8)	41 (26.5)	100 (31.2)	
Student	18 (10.9)	18 (11.6)	36 (11.2)	

Table 2: Frequency of cancer types among the cancer patients

Cancer	Frequency (%)
Cancer types	
Cervical	16.0 (9.7)
Breast	51.0 (30.9)
GIST	4.0 (2.4)
Leukaemia	68.0 (41.2)
Liver	3.0 (1.8)
Lung	2.0 (1.2)
Lymphoma	7.0 (4.2)
Ovarian	3.0 (1.8)
Pancreatic	2.0 (1.2)
Others	9.0 (5.5)
Cancer category	
Haematological	81 (49.1)
Solid malignancies	84 (50.9)
Total	**165 (100)**

The 9 cancer types classified as 'others' include colorectal tumour, neuroblastoma, right colonic tumour, head and neck cancer, kidney cancer, Wilm's tumour, prostate cancer, multiple myeloma and febrile neutropenia; GIST=Gastrointestinal stroma (GIST); leukaemia, lymphoma, multiple myeloma and febrile neutropenia were classified as haematological malignancies while the rest were classified as solid tumours

Table 3: Prevalence of oral *Candida* colonization in the case and control participants

Parameter	Case		Control	
	No (%)	*p* value	No (%)	*p* value
Females	44 (42.3)	0.226	33 (31.7)	0.055
Males	20 (32.8)		11 (18,0)	
Total	**64 (38.8)**		**44 (26.7)**	**0.0258***

* = statistically significant

Table 4: Prevalence of *Candida* species in relation to demographic characteristics of cancer patients

Characteristics	Colonized (%)	Not colonized (%)	Total	*p* value
Age group (years)				
≤ 10	1 (12.5)	7 (87.5)	8	0.217
11-20	1 (14.3)	6 (85.7)	7	
21-30	4 (33.3)	8 (66.7)	12	
31-40	13 (52.0)	12 (48)	25	
41-50	17 (37.8)	28 (62.2)	45	
51-60	11 (31.4)	24 (68.6)	35	
61-70	10 (47.6)	11 (52.4)	21	
>70	7 (58.3)	5 (41.7)	12	
Sex				
Male	20 (32.8)	41 (67.2)	61	0.226
Female	44 (42.3)	60 (57.7)	104	
Marital status				
Married	49 (42.2)	67 (57.8)	116	0.038*
Single	5 (17.2)	24 (82.8)	29	
Widowed	10 (52.6)	9 (47.4)	19	
Separated/divorced	0	1 (100)	1	
Level of education				
No formal education	3 (42.9)	4(57.1)	7	0.454
Primary	11 (47.8)	12(52.2)	23	
Secondary	16 (30.2)	37(69.8)	53	
Tertiary	33 (40.7)	48(59.3)	81	
Occupation				
Agriculture	2 (40.0)	3(60.0)	5	0.078
Clerical service	2 (100.0)	0	2	
Crafts	1 (12.5)	7 (87.5)	8	
Machine	1 (20.0)	4 (80.0)	5	
Unemployed	6 (54.5)	5 (45.5)	11	
Professional	14 (34.1)	27 (65.9)	41	
Retired	6 (37.5)	10 (62.5)	16	
Service and Trade	29 (49.2)	30 (50.8)	59	
Student	3 (16.7)	15 (83.3)	18	
Total	**64 (38.8)**	**101 (61.2)**	**165**	

* = statistically significant

Table 5: Frequency of *Candida* species isolated from cases and controls

***Candida* isolates**	**Case (%)**	**Control (%)**	**Total (%)**
Candida albicans	42 (55.3)	28 (54.9)	70 (55.1)
Candida krusei/Pichia kudriavzevii	26 (34.2)	9 (17.6)	35 (27.6)
Candida parapsilosis	3 (3.9)	12 (23.5)	13 (11.8)
Candida tropicalis	2 (2.6)	2 (3.9)	4 (3.1)
Candida/Nakaseomyces glabrata	1 (1.3)	0	1 (0.8)
Candida rugosa	2 (2.6)	0	2 (1.6)
Total	**76 (59.8)**	**51 (40.2)**	**127 (100.0)**

Table 6: Distribution of *Candida* species isolated from case and control participants with respect to colonization status

***Candida* species**	**Cases (%) (n=165)**	**Controls (%) (n=165)**	**Total (%) (n=330)**
Single agent			
C. albicans	33 (20.0)	20 (12.1)	53 (16.1)
C. krusei/P. kudriavzevii	20 (12.1)	7 (4.2)	27 (8.2)
C. parapsilosis	1 (0.6)	8 (4.8)	9 (2.7)
C. tropicalis	0	1 (0.6)	1 (0.3)
C. rugosa	1 (0.6)	0	1 (0.3)
Subtotal	55 (33.3)	36 (21.8)	91 (27.6)
Multiple (≥2) agents			
C. albicans + C. parapsilosis	1 (0.6)	3 (1.8)	4 (1.2)
C. albicans + C. tropicalis	1 (0.6)	1 (0.6)	2 (0.6)
C. albicans + C. krusei/P. kudriavzevii	6 (3.6)	4 (2.4)	10 (3.0)
C. albicans + C. parapsilosis + C. tropicalis + C/N. glabrata + C. rugosa	1 (0.6)	0	1 (0.3)
Subtotal	9 (5.5)	8 (4.8)	17 (5.1)
Total	**64 (38.8)**	**44 (26.7)**	**108 (32.7)**

Table 7: Antifungal Susceptibility patterns of the *Candida* isolates

Antifungal agent/ Interpretation	***C. albicans* (n=69)**	**non *albicans Candida* (n=55)**						**Total (n=124)**	***p* value**
		C. krusei/P. kudriavzevii	***C. parapsilosis***	***C. tropicalis***	***C/N. glabrata***	***C. rugosa***	**Total**		
Voriconazole									
S	22 (31.9)	27 (75.0)	10 (83.3)	-	-	1 (50.0)	38 (69.1)	60 (48.4)	<0.001*
I	0	3 (8.3)	-	-	-	-	3 (5.5)	3 (2.4)	
R	47 (68.1)	6 (17.6)	2 (16.7)	4 (100)	1 (100)	1 (50.0)	14 (25.5)	61 (49.2)	
Fluconazole									
S	18 (26.1)	26 (72.2)	8 (66.7)	0	0	0	35 (63.6)	53 (42.7)	<0.001*
I	4 (5.8)	3 (8.3)	2 (16.7)	0	0	0	5 (9.1)	9 (7.3)	
R	47 (68.1)	7 (19.4)	2 (16.7)	4 (100)	1 (100)	4 (100)	15 (27.3)	62 (50.0)	
Itraconazole									
S	17 (24.6)	28 (77.8)	10 (83.3)	0	0	1 (50)	39 (70.9)	56 (45.2)	<0.001*
I	1 (1.4)	0	0	0	0	0	0	1 (0.8)	
R	51 (73.9)	8 (22.2)	2 (16.7)	4 (100)	1 (100)	1 (50)	16 (29.1)	67 (54.0)	
Amphotericin B									
S	43 (62.3)	12 (33.3)	3 (25)	1 (25)	0	0	16 (29.1)	59 (47.6)	<0.011*
R	26 (37.7)	24 (66.7)	9 (75)	3 (75)	1 (100)	2 (100)	39 (70.9)	65 (52.4)	
Caspofungin									
S	58 (84.1)	22 (61.1)	8 (66.7)	4 (100)	1 (100)	1 (50)	36 (65.5)	94 (75.8)	0.085
R	11 (15.9)	14 (38.9)	4 (33.3)	0	0	1 (50)	19 (34.5)	30 (24.2)	
Nystatin									
S	66 (95.7)	34 (94.4)	11 (91.7)	4(100)	1 (100)	2 (100)	52 (94.5)	118 (95.2)	0.980
I	3 (4.3)	2 (5.6)	1 (8.3)	0	0	0	3 (5.5)	6 (4.8)	
Multi-drug resistant									
Yes	22 (31.9)	14 (37.8)	5 (41.7)	3 (75.0)	1 (100)	2 (100)	24 (43.6)	53 (42.7)	0.01*
No	47 (68.1)	23 (62.2)	7 (58.3)	1 (25.0)	-	-	31 (56.4)	71 (57.2)	

S=Sensitive, I = Intermediate (Susceptible dose-dependent), R = Resistant; *p* values represent differences in susceptibility between *Candida. albicans* and non-*albicans Candida* species; * = statistically significant at $p<0.05$ *

Antifungal susceptibility pattern of isolated *Candida* species:

Candida albicans were more resistant than non-*albicans Candida* species to the azoles. However, the reverse was observed for other antifungal agents. The frequency of multi-drug resistance (MDR) was significantly higher (p=0.01) in non-*albicans Candida* species (43.6%, n=24) than *C. albicans* (31.9%, n=22) (Table 7).

Discussion:

Candida species was significantly more prevalent in the oral cavity of cancer patients (38.8%) compared to the healthy controls (26.7%), which is comparable to that reported by Bakki et al., (19). It is opined that this increase in oral *Candida* colonization might have resulted from their states of immune deficiency. In the cancer patients, the highest prevalence was observed among the elderly of age 71 years and above (58.3%) and this agrees with previous findings (20-22). This should be expected as old age is also a factor that contributes to weakened immunity and elderly people may be poor in oral hygiene. Good oral hygiene should be encouraged in this set of people so as to prevent susceptibility to *Candida* infection. Regular surveillance for colonisation by *Candida* species should also be carried out on this group of people. Higher prevalence of *Candida* species was also observed in females (42.3%) than in males (32.8%) among the cancer patients, which agrees with the findings of Marak and Dhanashree (23), who reported a higher incidence of clinical *Candida* species in females (54%) than in males (45%). Good hygiene, especially regular practice of hand washing must be imbibed by women as most women carry *Candida* species in their genital areas.

Based on marital status, the highest prevalence of *Candida* species seen among the widowed (52.6%) is well understandable since most of the widows naturally fall into the age group of the elderly (22). In this study, the level of education had no significant impact on rate of *Candida* species colonization, which agrees with previous findings (24). The highest prevalence seen among the clerical staff (100.0%), followed by those in service and trade (48.0%) may be due to horizontal transfer of the yeasts through constant human interactions. In the study, leukaemia (41.2%) was the most frequent cancer type followed by breast cancer (30.9%). This agrees with the findings of a previous research (25). Oral colonization by single *Candida* species of 33.3% (n=55) and multiple species of 5.5% (n=9) among the cancer patients in the study agrees with the report of Aslani et al., (26). *C. albicans* was the most commonly isolated *Candida* species from both the cancer patients (55.3%) and the controls (54.9%). This is similar to a previous study by Lone et al., (21) who reported that *C. albicans* (58.0%) was the predominant species isolated from cancer patients.

Candida isolates showed least susceptibility to fluconazole (42.7%), which agrees with the findings of Soliman et al., (27) who reported that the sensitivity to fluconazole among *Candida* species isolated from clinical samples was 41.6%. Fifty percent of the *Candida* isolates in our study were resistant to fluconazole, similar to the study of Waikhom et al., (24) who reported that 48.1% of *Candida* species isolates were resistant to fluconazole. Higher resistance rate to fluconazole was observed among *C. albicans* (68.1%) compared to the non *albicans Candida* species (25.5%). The only *C./N. glabrata* isolate (100.0%) in this study was resistant to fluconazole, which agrees with previous findings (28). This is most likely due to the fact that this yeast species possesses intrinsic resistance to fluconazole (29). All *C. tropicalis* (100%) isolates were resistance to azoles, which agrees with the reports of Jayachandran et al., (30). *Candida parapsilosis* was highly sensitive (85.7%) to itraconazole, which agrees with the study of Lyon et al., (31) who reported 90% of *C. parapsilosis* isolated from denture wearers to be susceptible to itraconazole. Most *C. krusei/P. kudriavzevii* in this study were susceptible to azoles, which contrast previous report that the yeast is intrinsically resistant to azoles (32). This is because some strains of *C. krusei/P. kudriavzevii* might have their genes mutated.

Resistance rate to itraconazole in all the *Candida* species was 54.0%. This agrees study of Tsega and Mekonnen (33) who reported 57.3% of *Candida* species isolated from pregnant women were resistant to itraconazole. In this study, resistance rate to voriconazole, a third-generation azole, was 48.8%. This disagrees with the findings of Bitew and Abebaw (34), who observed that all isolated *Candida* species isolated from some Ethiopian women with vulvovaginal candidiasis were 100% susceptible to voriconazole. Moreover, significantly higher (p<0.001) resistance rates of 68.1%, 68.1% and 73.9% were observed among *C. albicans* than non-albicans *Candida* species of 25.5%, 27.3% and 29.1% to voriconazole, fluconazole and itraconazole respectively. This contrasts the study of Jayachandran (30) who reported that non-*albicans Candida* species demonstrated higher resistance to fluconazole and itraconazole

than *C. albicans.* The increase in resistance of *C. albicans* to the azoles is probably due to over exposure to this class of antifungal agent.

Worthy of note is the increasing resistance to fluconazole shown in our study when compared with previous studies (20,26, 35-37). This situation might have arisen from frequent administration of fluconazole as first line antifungal drug in the treatment of candidiasis (38). The reduced *in vitro* activities of the azole antifungal agents in this study agree with the findings of Mba and Nweze (39) who reported that *Candida* species demonstrated multi-azole resistance. It was observed that a *Candida* species which was resistant to particular azole was most often resistant to the rest of the azole drugs, which agrees with Owotade et al., (40) who reported that *Candida* species that are resistant to a particular azole are likely to be resistant to other azole drugs. Therefore, other antifungal agents apart from azole should be administered to a patient who does not respond to an azole (40).

Due to the emergence of resistance to azole among *Candida* species, the echinocandins such as caspofungin are now the first-line therapeutic choice in the treatment of invasive candidiasis in some countries (41). Echinocandins generally demonstrate greater activity against *Candida* species than the azoles (42,43). Although, these class of drugs are not available in Nigeria, only 75.8% (n=94) of all the *Candida* isolates in our study were susceptible to caspofungin, which is similar to the finding of a previous study (44), although contrast the report of another study (45). Resistance to caspofungin in *Candida* species is known to be rare. Notwithstanding, certain *Candida* species such as *C. tropicalis* have been reported to demonstrate resistance to this drug. In our study, 25.0% (n=19) of all the *Candida* species were resistant to caspofungin, which agrees with the report of a study by Aslani et al., (26), while 15.9% (n=11) of the *C. albicans* isolates were resistant to caspofungin in agreement with the study of Mahmoudabadi et al., (44) who reported 13.04% (n=3) clinical isolates of *C. albicans* to be resistant to caspofungin. All the *C. tropicalis* were susceptible to caspofungin in our study, which is contrary to the findings of Pasquale (46) who reported the first incidence of caspofungin resistance in *C. tropicalis.* About 33.3% (n= 4) of *C. parapsilosis* were resistant to caspofungin, which is similar to the findings of Cuenca-Estrella et al., (47) who reported *C. parapsilosis* isolates from China and Malaysia to be resistant to caspofungin. Resistance to caspofungin despite the fact that there was no prior exposure might be as result of intrinsic or cross resistance to drugs in *Candida* species.

The susceptibility results for polyene class of antifungals (amphotericin B and nystatin) against the *Candida* isolates showed that only 47.6% were susceptible to amphotericin B, similar to the findings of Soliman et al., (27) who reported that 50.0% of *Candida* species isolated from clinical samples were susceptible to amphotericin B. However, our finding result disagrees with several previous reports where all tested *Candida* isolates (100%) were susceptible to amphotericin B (23,48). Drug misuse and overuse might be the cause for the increased resistance. Among the antifungal agents tested, nystatin was the most effective while the azoles (fluconazole, itraconazole and voriconazole) were the least effective. This is in line with the findings of Ambe et al., (49) who reported that *Candida* species demonstrated highest sensitivity to nystatin and highest resistance to the azoles (ketoconazole and fluconazole). However, earlier reports showed that all *Candida* species isolated were susceptible to nystatin (50,51). Worthy of note is the occurrence of intermediate susceptibility to nystatin in our study, which also raises a concern about emerging resistance to nystatin, that appears to be the only remaining potent antifungal drug of choice available for treating *Candida* infections. Misidentification and misappropriation of drugs often lead to decreased susceptibility to antimicrobial agents.

In this study, multi-drug resistance was most frequently observed in *C. rugosa* (100.0%, n=2) and *C./N. glabrata* (100%, n=1), followed by *C. tropicalis* (75.0%, n=3) and the least was among *C. albicans* (31.9%, n=22). Prolonged use of different antifungal agents in various clinics has led to an increase in multidrug resistant *Candida* species such as *C./N. glabrata*. Multidrug resistance is a major global healthcare challenge which is an impediment to successful treatment of infected patients (52). Antimicrobial stewardship, regular surveillance for *Candida* colonization, precise identification, sensitivity testing and appropriate treatment must be regularly practised in the management of immune suppressed individuals so as to prevent systemic candidiasis which can result in increased debility and mortality among this set of individuals.

Conclusion:

In this study, it was generally observed that *Candida* species were more prevalent in the oral cavities of cancer patients than healthy persons. Cancer therapies may contribute to increased oral colonization by *Candida* species in cancer patients. Nystatin

remains the drug of choice in the treatment of *Candida* infection.

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Contribution of authors:

OEA, JSG, OFO, OFJ, OBW and OO designed the project; OEA carried out the research; OEA, JSG, OFO, OFJ, OBW, OO, and GPT reviewed the manuscript, and JSG and OFJ supervised the research. All authors approved the final manuscript submitted for publication.

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Authors declare no conflict of interest

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