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RESEARCH ARTICLE

FREQUENCY RATE OF ORAL CANDIDIASIS AMONG PATIENTS ON ONCOLOGY MANAGEMENT AT KHARTOUM ISOTOPE AND RADIATION TEACHING HOSPITAL.

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Abstract

Background: Oropharyngeal candidiasis is one of the common manifestations seen in cancer patients on cytotoxic therapy and invasion into deeper tissues can occur if not treated promptly and little is known about the epidemiology of oral *Candida* colonization and infection in immunocompromised patients in developing countries. Thus this study was carried out to determine the frequency rate of oral candidiasis among patients on oncology management at Khartoum Isotope and Radiation Center.

Method: A total of 168 cancer patients under treatment of chemotherapy and /or radiotherapy were taken as100 out-patients and 68 inpatients control group. Those were examined for oral candidiasis. For all patients, the clinical diagnosis had to be confirmed microbiologically by the presence of yeasts and / or hyphae or pseudohyphae on potassium hydroxide - treated smears of oral swabs. Oral samples were obtained and cultured on Sabouraud's dextrose agar.

Result: Out of 69 *Candida* isolates, total colonization was prevalent in 46(66.7%) and oral candidiasis in 23(33.3.3%) of all cancer patients, representing 3(8.8%) and 20(57.1%) infection among out-patients and in-patients respectively.

Candida albicans was significantly more common than *nan – candida albicans* in both study group (76.5% vs 32.5%) and control group (68.5% vs. 31.4%).

Amongst the cancer group, 147(87.5%) had solid organ malignancy, 21(12.5%) had hematological malignancy.

High frequency of *Candida* isolates were detected among females, breast cancer, with chemotherapy treatment, among those who were from North Sudan and South Dar-for and among patients who belong to Al-gaalia tribe.

Conclusion: Oral candidiasis is more common among cancer patients with considerable risk to hospitalized patients.

Though *Candida albicans* was found as the most common species but *non-albicans candida* species are appearing as emerging pathogens as well.

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Introduction:-

Within the past two decades, *Candida* species have emerged as major human pathogens and are currently the fourth most common cause of nosocomial infection [1].

Nosocomial infections constitute a serious public health problem, and are among the major causes of morbidity and mortality in humans, leading to increased hospitalization time and, consequently, generating high costs for patient treatment [2]. Infections caused by *Candida* species have been increased dramatically worldwide due to the increase in immunocompromised patients [3].

Oropharyngeal candidiasis is a common infection in cancer patients and currently rank the most common human fungal disease [4].

Candida species are common members of the oral microflora and are generally regarded as being commensals. However, they are able to cause a range of opportunistic infections, referred to as candidiasis [5, 6].

The prevalence of diseases caused by *Candida* spp. has increased in recent years, mainly due to the increasing number of immunocompromised patients. *Candida albicans* is still the predominant species isolated, and it has the potential to infect virtually any tissue within the body. However, it is predominantly found on the oral and vaginal mucosa [7, 8].

The prevalence of oral candidiasis in various countries varies among studies according to location, age of the patients, and the site sample, and has been reported to range from 20- 75% [9].

Over the years an incidence of 7.2– 52% has been reported depending on treatment interventions and the type and stage of the malignancy [10].

Majority of oral infections are due to *C. albicans* but *non-albicans* strains such as *C. glabrata* and *C. tropicalis* have increasingly been implicated in causing disease [11].

The colonized *Candida* can invade the underlying mucosa and enter the blood stream leading onto disseminated disease with considerable morbidity and mortality if not treated promptly. Fluconazole is one of the first line drugs used for the treatment of oral candidiasis in cancer patients [12, 13]. Most studies place the crude mortality rate due to *C. albicans* infections at around 30%–40% , [14, 15] but some have estimated this to be as high as 46%–75% [16].

A systematic review indicated that the weighed mean prevalence of clinical oral fungal infection during chemotherapy is 38% [17]**,** and the most common forms of intraoral candidiasis reported in oncology patients are pseudomembranous and erythematous candidiasis[18, 19]. Pseudomembranous candidiasis can usually be diagnosed on the basis of its characteristic clinical appearance and may be accompanied by burning pain and taste changes. The appearance of erythematous candidiasis is relatively nonspecific, and laboratory testing may be needed to confirm the diagnosis. It may be accompanied by a burning sensation of the affected tissues [20].

Chemotherapeutic agents and therapeutic radiation disrupts the mucosal banner of the mouth, leading to severe oral mucositis, gingivitis, oral candidiasis, cellulitis and viral mucosal eruptions [21]. The oral mucositis or inflammation of the oral mucosa is painful and is characterized by erythema, edema, and mucosal shedding, which can lead to ulceration and secondary infection [22].

The irradiation-induced histological changes leading to oral mucositis, together with salivary quantitative and qualitative changes, have been reported to facilitate yeast growth [23].

Oral candidiasis presents as a removable white pseudomembrane or erythematous patch on the tongue, palate and labial commissures. It causes taste alterations, mucosal soreness and oral burning sensations. Heavy accumulations of candida may dislodge causing esophagitis, fungemia and pose aspiration risk to the patient [24].

The routine oral examination of cancer patients has revealed a greater incidence of *Candida* infections than that in most types of patients. Almost all surveys on fungal infections in cancer patients come from USA, Europe, and other developed countries, and little is known about this problem in developing countries, [1] particularly Sudan. For the first time we report on occurrence rate of oral Candidiasis among cancer patients at Isotope and Radiation center – Khartoum.

Materials and Methods:-

It was a cross-sectional, case control study conducted in a period of 2015 to 2016. The study involved 100 cancer patients (Out-patients) as case study and 68 cancer patients (inpatients) as control groups, both group were under treatment of chemotherapy and/or radiotherapy in Radiation and Isotopes Centre Khartoum. Patients on antifungal therapy for past two weeks were excluded from the study. Both groups with a mean age of 48 years old, the patients were explained and informed consent was obtained from the patients. The demographic data, origin, type of cancer and treatment were considered in this study.

A total of 100 samples from cases and 68 from in-patients controls were included in the study. An examination of the oral cavity of the patients was performed and a sample from tongue, buccal mucosa and labial sulcus was taken with a sterile pre-moistened swab.
All samples were processed for yeast isolation in Microbiology laboratory following collection.

Oral *Candida* colonization was defined as presence of yeasts in the oral cavity irrespective of signs and symptoms. Oral candidiasis was defined as presence of *Candida* spp. in the oral cavity together with signs and symptoms of oral candidiasis like inflammation/mucositis and/or presence of white plaques confirmed microbiologically by the presence of yeasts and/or hyphae or pseudohyphae on potassium hydroxide–treated smears of oral swabs [25].

For all patients, the clinical diagnosis was confirmed microscopically by the presence of yeasts and hyphae or pseudohyphae on 10% potassium hydroxide (KOH) preparation of oral swabs. Swabs were streaked onto Sabouraud's dextrose agar (SDA) to which chloramphenicol (0.05g/l) was added., which is the most useful and popular primary culture media [26]. Then the Plates were incubated at 37^0C for 24-48 hours, and *Candida* colonies appeared as cream coloured smooth or rough, shiny or dull and convex.

According to classification of oral candidoses [27], identification of *Candida* species was made using direct microscopy of the Gram stained smears that show characteristic rounded , or oval budding cells of yeast blastospores (yeast form) with or without the hyphal phase, which can be distinguished readily from bacteria by their greater size (3-6 μm) , budding , oval shape and pseudohyphae,.Identification of *Candida* species from growth in SDA media was done by germ tube test which it was perform to identify *C.albicans*, and to differentiate *C.albicans* from *non albicans* groups. Lightly touched single yeast colonies with sterile wire loop from the culture plate was inoculated in fresh human pooled serum and incubated at 37^0C for 2-3 hours. The wet mount preparation showed germ tube which is a hyphal projection, as mentioned in [28].

Statistical analysis:-

Data analyzed using Spss 21 (Statistical package for social sciences) with reference p-value (.05), P-value $\leq$.05 conceder as significant result. Frequencies and percent obtained in frequency tables, chi-square testfor goodness of fitused to test these frequencies. The relations between variables tested using cross tables and chi-square (Fisher exact)test for independence.

Ethical consideration:-

An approval was taken from the University, Faculty and Department of Medical microbiology management.
Consent was taken from Ministry of health, hospital and participants before taking samples.-

Results:-

The subject (168) involved in this study were cancer patients with chemotherapy and/or radiotherapy treatment, they represented (100) outpatients and (68) in-patients control group. The oral swab specimens were collected from 168 cancer patients and examined by cultural techniques. *Candida species* were isolated from 69 (41.1%) patients while 99(58.9 %) patients showed no growth. The culture result among the out-patients and control group as in figure (1).

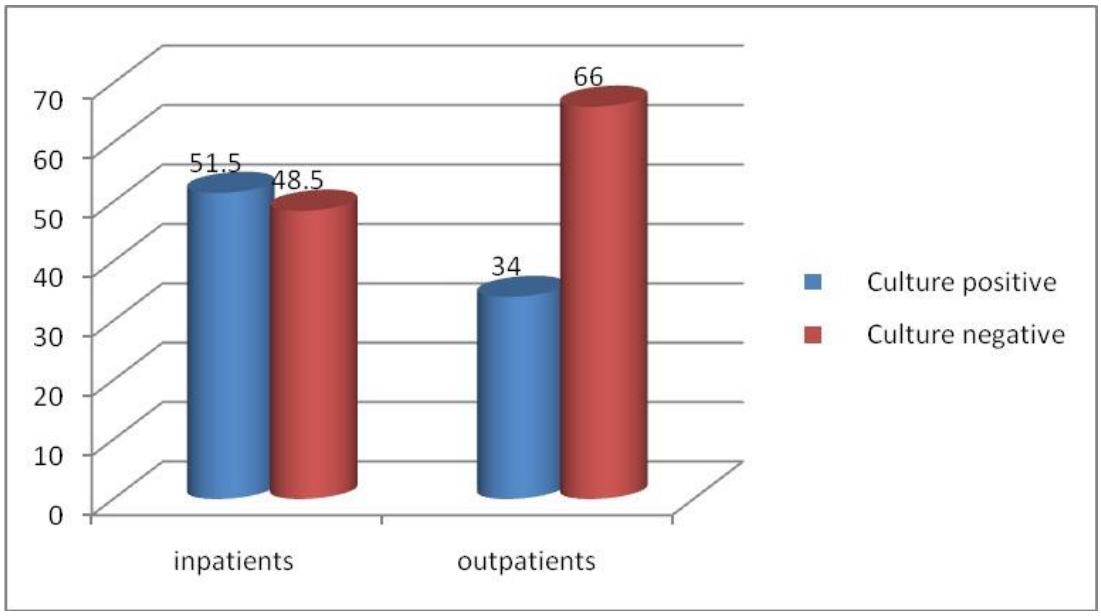

Figure 1:- Culture result according to the out-patients and in-patients control group.

The colonized *Candida* can invade the underlying mucosa and enter the blood stream leading onto disseminated disease. For all cancer patients the prevalence of oral candidiasis was 23(33.3) while the prevalence of oral colonization was (66.7), and significantly the infection was more common among inpatients group than out-patients.(p value <0.05) (Table 1).

Table 1:- Frequency of oral infection and colonization

	Symptoms Infection)	**No symptoms (Colonization)**	**Total**
	Positive No %	**Positive No %**	**No %**
Out-patients	3 (8.8)	31 (91.2)	33 100
In-patients	20 (57.1)	15 (42.9)	35 100
Total	23 (33.3)	46 (66.7)	69 100

In the present study it was found that *C.albicans* was significantly (P-<0.05) representing the most common isolated organism among both groups. (Figure 2)

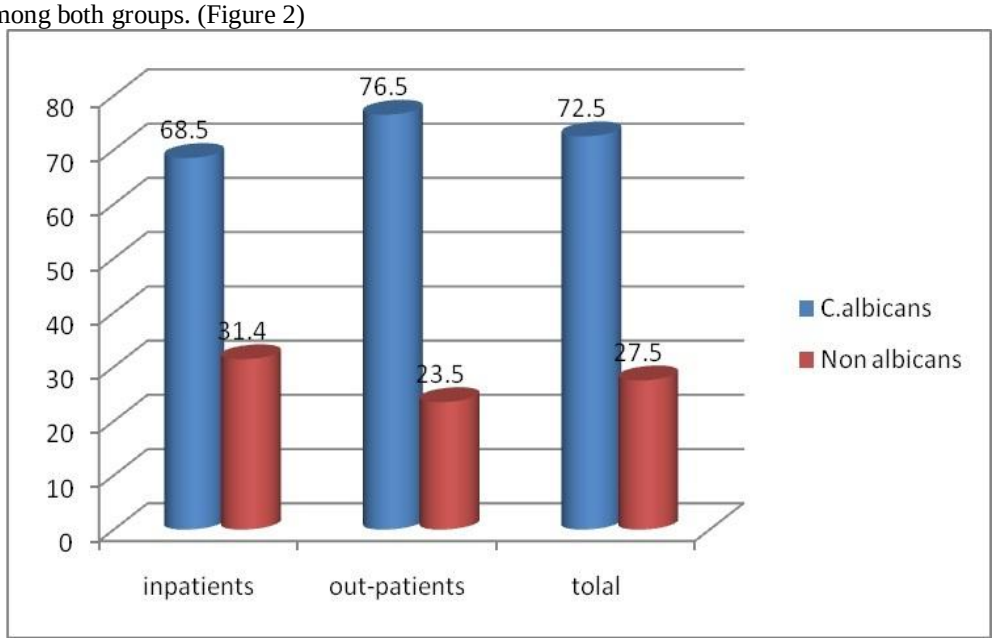

Figure 2:- Frequency of isolated *Candida* spp among out-patients and in-patients control group.

Among the examined 76 (45.3%) males and 92 (54.7%) females, *Candida* species were found insignificantly more prevalent among females 42(45.5%) than males 27(35.5%). Similar in the inpatients group which represented 52.5% vs 44.4%.whereas in the outpatient group showed 34.3% males and 33.3% females.

The age range of patients in study group was 15 to 85 years with mean age of 48.4 years; patients were classified into 4 groups according to the age group. (Table 2)

Table 2:- frequency of *Candida* isolates among cancer patients according to age group

			Candida		Total
			Positive	Negative	
Age	15-33 Year	Count	16	12	28
		% within Candida	23.2%	12.1%	16.7%
	34-52 Year	Count	27	44	71
		% within Candida	39.1%	44.4%	42.2%
	53-71 Year	Count	22	40	62
		% within Candida	31.9%	40.4%	36.9%
	< 72	Count	4	3	7
		% within Candida	5.8%	3.0%	4.2%
Total		Count	69	99	168
		% within Candida	100.0%	100.0%	100.0%

P-value Chi square 0.187

Candida infection was more in patients treated with chemotherapy alone and least infection was shown in patients treated with radiotherapy (Table 3).

Table 3:- Distribution of isolated *Candida* spp according to type of cancer treatments

Treatment		NO	%
Categories	Chemotherapy & Radiotherapy	15	21.7
	Chemotherapy	47	68.1
	Radiotherapy	7	10.1
	Total	69	100.0

P-value of chi-squared for goodness of fit=.000

The present study explained statistically significant distribution of oral candidiasis among cancer patients according to type of cancer (Figure 3).

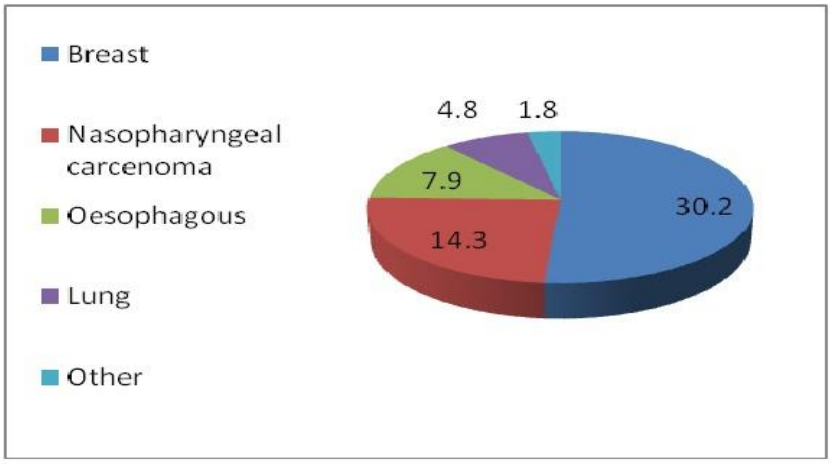

Figure 3:- Percentage of *Candida* spp according to the cancer sites in the patients tested.

According to the environment and inherited genes of the Sudanese State, although all patients were treated in Isotope and Radiation Center are coming from different State. The high numbers of examined patients are from Khartoum state followed by Gezira State (Table 4). And according to the tribes more infection in Al-Gaalia tribe 6 out of 69 (8.8%) followed by Zagaoa 4 out of 69 (5.9%).

Table 4:- Frequency of oral Candidiasis among cancer patients according to origin

States		positive		total	
		No	%	No	%
The first 12 prevalent States	Khartoum	7	10.3	20	12.0
	Gezira	3	4.3	18	10.8
	North sudan	9	13.2	18	10.8
	South Dar-for	9	13.2	16	9.6
	White Nile	8	11.8	13	7.8
	Nortn kurdofan	4	5.9	13	7.8
	South Kurdofan	6	8.8	11	6.6
	North Dar-for	2	2.8	9	5.4
	Al-gadarif	1	1.4	8	4.8
	Sinar	5	7.4	8	4.8
	Kasala	4	5.9	6	3.6
	West Dar-for	2	2.8	6	3.6

P-value of chi-squared for goodness of fit=.000

Discussion:-

In the present study it was found that *Candida* species were isolated from 69 (41.1%) patients while 99(58.9 %) patients showed no growth. Also Lihua Xu, *et al*., [29] found that oral infection was prevalent in 46% (391/850) of all cancer patients. Other studies have reported the incidence of oral candidiasis ranging from 7 to 52% in cancer patients on chemotherapy and/or radiotherapy [30].

The present study revealed the frequency of *Candida* isolates to be significantly more prevalent in in-patients than out-patients group (51.5% vs. 34%). Similar finding were obtainedby Hanan, *et al*. [31].

Regarding the infection and colonization it was found that among the total examined patients, the prevalence of oral candidiasis was 33.3 while 66.7% was colonization. Relatively similar result reprted by Mohd, *et al*. in (2014), [32] they found the total colonization to be prevalent in 50% and oral candidiasis in 30% of all cancer patients. Also Rajesh, *et al* [33] found that in a systematic review of oral fungal infections in patients receiving cancer therapy, the weighed prevalence of clinical oral infection (oral candidiasis) and oral colonization during treatment was 39.1% and 72.2% , respectively.

In a study done by [31]. It was found that in-patients cancer group harboured *Candida* spp at significantly high levels than out patients. This study clearly demonstrated similar result that oral candidasis was significantly higher among in-patients (42.9%) (P value <0.05) than out patients group (8.8%), while colonization are more common in the out patients group Table (1).

Several previous works [31, 28, and 34] that studied the prevalence of oral *Candida* spp demonstrated that *Candia albicans* was the most prevalent organism. Similarly the present study revealed *Candida albicans* to be the most common organism both among out-patients and in-patients control group (76.5% vs. 68.5%), respectively. also Shaheen, *et al*, found that *C. albicans* to be the only species recovered from non hospitalized patients(100%) while in hospitalize patients it was only 56%.

Oral infection was insignificantly more common among females than males (p <0.05). This may be due to increase number of females than males in this study. This finding is in agreement with the study of Intisar, *et.al* [35] who studied a total of 6771 cases of cancer incidence, they found females cases as 53.8% and males (46.2%).

The higher prevalence of oral candidiasis was found among the age group (34-52) year followed by the age group 53-72 years. This may be due to the fact that, the most cancer patients were occupaied in this group, as reported by

study, [35] that the higher incidence cases of cancer were recorded among Khartoum residents in 2009–2010 were between 25-54 years. Similar previous finding found *C. albicans* present in the oral cavities of patients belonging to age group of 40 - 60 years than in any other age group [36].

Amongst the cases (n=168), 147 (87.5%) had solid organ malignancy and 21 (12.5%) patients with hematological malignancy. Breast cancer patients represented the higher group among different types of cancer in Sudan [36] this agrees with the fact that this type of cancer is a worldwide distribution in different countries. It was found the high frequently of *Candida* spp. appeared in patients with breast cancer, which is in accordance to other investigation [37]**,** this is in agreement with this study.

The current study showed significant increased percentage (63.9%) of *Candida* isolates among chemotherapy treated patients as most of the cases 114 (67.9%) under chemotherapy treatment only. It is well known that cancer and chemotherapy result in immunosuppression which gives opportunity for emergence of *Candida* infection. The outcome is the immune dysfunction and mucosal damage which promote yeast infections such as mucositis, xerostomia and candidiasis [38, 39]. It is well known that prolonged use of chemotherapy may lead to neutropenia, disruption of mucosal barrier and overall damage to cell mediated immunity which increases the risk of infection. [40].

Although the high number of cancer patients in the current study were represented at Khartoum State followed by Gezira State. Oral candidiasis was found more common among patients who are from North Sudan and South Dar-for (13.2%) equally. and among those who belong to Al-gaalia tribe (8.8%) table (4). This may be due to either inherited genes or environmental factors, thus further studies must be carried out to enrich this field.

Conclusion:-

In the present study we demonstrate that *C. albicans* and other *Non- C. albicans* species are associated commonly with the oral cavity in immounocompromised patients. Oral colonization and infection by *Candida* spp. is a matter of concern especially among in-patients group as multiple risk factors contribute to such a scenario in this vulnerable group.

The incidence of this yeast varies depending on cancer type, sex, and age; type of cancer treatment, origin and tribe of patients.

The frequent occurrence of *Candida* species in oral cavity of immounocompromised patients indicates a need for effective management for the isolation and identification of this yeast prior to any treatment.

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