

## Research Article

# Predictors of Candidemia infections and its associated risk of mortality among adult and pediatric cancer patients: A retrospective study in Lahore, Punjab, Pakistan

Hafiz Muhammad Bilal<sup>1\*</sup>, Shazia Ayaz<sup>2</sup> and Neelam Iqbal<sup>1</sup><sup>1</sup>MBBS, Nishtar Medical College, Multan, Pakistan<sup>2</sup>MBBS, Ghazi Khan Medical College, D.G. Khan, Pakistan

**\*Address for Correspondence:** Hafiz Muhammad Bilal, MBBS, Nishtar Medical College, Multan, Pakistan, Tel: 092-302-9579060; Fax: 092-62-9255243, Email: drbilal280nmc@gmail.com

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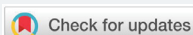
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**Keywords:** Cancer patients; Hematological malignancies; Predictors; Albican; Non-albican; Candidemia

**Abbreviations:** BSI: Bloodstream Infections; LMIC: Low and middle income countries; ICU: Intensive Care Units; TPN: Total Parenteral Nutrition



## Abstract

**Objectives:** As the cancer patients are at higher risk of premature deaths due to candidemia. So, the present study aims to evaluate the predictors of candidemia along with its outcomes among hospitalized adults and pediatric cancer patients.

**Methods:** A retrospective study was conducted at a tertiary care cancer hospital in Lahore, Pakistan. The data was collected from the medical records of all the patients who were found positive for *Candida* species between 1<sup>st</sup> January 2017 and 31<sup>st</sup> June 2017. Data were analyzed by using Statistical Packages for Social Sciences (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and Microsoft Excel (MS Office 2010).

**Results:** Overall, 135 patients were detected with candidemia. Based on blood culture test results, it was found that out of 100 cultures positive for any microorganism there were 2 cases of candidemia. Multivariate analysis revealed that hematological malignancies (AOR: 2.1), and shock (AOR: 9.1) were significantly associated with high risk of mortalities during the index hospitalization, while risk of mortality among cancer patients suffering from *Candida albican* infection (AOR: 0.47) and those who were administered with antifungal agent after sensitivity report of the fungal culture (AOR: 0.2) was significantly less. Also, there was no significant association of empiric therapy of antifungal agent with the risk of mortality before a positive culture found ( $p > 0.05$ ).

**Conclusion:** Although, no risk factor was found to be associated significantly with candidemia among cancer patients. But hematological malignancies, non-albican candidemia and shock were predictors of higher risk mortality during index hospitalization

## Introduction

The bloodstream infections (BSI) caused by Fungi are one of the major factors responsible for premature death of hospitalized cancer sufferers. Among all the Fungi, the causative agents for most of the nosocomial infections are the members of genus *Candida*. These microorganisms have worsen the situation by causing an increment up to 50% in mortality rate of cancer patients [1]. It is evident from the previously published studies that candidemia accounts for 10-50% of the mortalities among hospitalized cancer patients [2, 3]. Besides mortality rate, these infections not only lengthen the stay in hospitals and intensive care units (ICU) but also make the treatment expensive [4].

The blood culture test predicts that *Candida albican* is responsible for fungal infections in most of the immune competent patients. Also species other than albican are

responsible for causing infections among cancer patients [5]. Although these infections are prevailing in many low and middle income countries (LMIC). But limited data regarding epidemiology of BSI caused by *Candida* have been published till date. Particularly cancer patients have fall a pray into these infections because of malnutrition, late diagnosis and inadequate strategies of controlling these infections [6]. The number of cancer patients is continuously increasing in many LMIC, so candidemia is assumed to be the prime factor responsible for premature morbidity and mortality among these patients. Therefore, the present study aimed to evaluate the predictors and outcomes of candidemia among hospitalized cancer patients in Pakistan.

## Materials and Methods

### Study design and setting

A retrospective study was conducted in a cancer specialty named as Shaukat Khanum Memorial Cancer Hospital & Research Centre (SKMCH&RC), Lahore, Pakistan. Data were collected between 1<sup>st</sup> January 2017 and 31<sup>st</sup> June 2017. The selected setting was a non-profit organization providing referral base cancer specialty to the patients from all over the Pakistan. The characteristics of selected study setting have been summarized in Table 1 [7]. The SKMCH&RC is a well-equipped hospital with electronic database. All the medical records of patients can be assessed online by using International Classification of Diseases versions 9 or 10 (ICD-9 / ICD-10) codes or keywords.

### Study population and sample size

The records of 6,397 cancer patients were securitized. The patients were included in the study if their blood culture tests were found positive for any microorganism, were not on the last stage of malignancy, had not been found to be the victim of any infectious disease like acquired immunodeficiency syndrome (AIDS) and not administered with immunosuppressants. The records of 927 patients were fulfilled our inclusion criteria and consequently selected for the study.

### Data collection

A data collection tool was used to collect the data. The questionnaire was structured and consisted of 4 parts: 1) characteristics of the patients, 2) diagnosis detail (detection of candida specie and the type of cancer), 3) therapeutics detail (use of total parenteral nutrition (TPN), dose and type of administered steroids, antibiotics and chemotherapeutic agents in the preceding three months, and use of central venous catheter, 4) health status of patients (neutropenia status, and outcomes of hospitalization). If the same patient hospitalized due to candida infections at different time intervals then each occasion was treated as a separate episode of hospitalization. The time period was divided into three categories. First category is from January to February, second is from March to April and third is from May to June. The blood culture test was performed on each patient who were suspected for candidemia and bacteremia. The conventional manual blood culture system was used for processing the blood samples and the reporting was done according to standard microbiological

**Table 1:** Characteristics of study settings.

Characteristics	N
Number of Beds	195
New registrations	10,203
Total Outpatient visits last year	236,351
Admissions	12,576
Total patients receive chemotherapy last year	52,843
Total patients receive radiotherapy last year	65,759
Total patients underwent surgery last year	13,817
Total number of pathological test performed last year	5,015,237
Total number of imaging studies performed last year	174,932

techniques. If the culture was found positive for yeast then it was further investigated through the germ tube test and testified as candida albican or candida non-albican. Only two antifungal agents Amphotericin B deoxycholate and fluconazole were available during the study period.

### Data analysis

The characteristics of the study population were summarized using descriptive statistics. Chi-square, Fisher's exact tests and multivariate logistic regression analyses were used to compare categorical variables and to test the association between characteristics and outcomes of mortality. The final model for estimation of adjusted odds ratios (AOR) was developed through forward selection. All statistical tests were 2-sided, with a type 1 error level of 0.05. Data were analyzed by using Statistical Packages for Social Sciences (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and Microsoft Excel (MS Office 2010).

### Definitions

**Bacteremia:** If the bacteria was identified in blood during culture test.

**Candidemia:** If the candida specie was identified in blood during blood culture test.

**Shock:** The state of medical emergency when systolic blood pressure (BP) was <90mmHg, diastolic BP was <60mmHg and / or patient was administered with ionotropic agents to maintain BP.

**Duration of stay:** The time period from the first day when blood culture test was found to be positive for candida specie till the day of discharge or death.

**Index hospitalization:** When a patient was first time admitted to the hospital.

### Ethics approval

Ethical approval was obtained from the Medical Research Ethics Committee (MREC) of Nishtar Medical College, Multan (Reference: 10-2016/REC, dated October 22, 2016). The permission to conduct this study was also obtained from the administrators of the SKMCH&RC.

### Results

Among all the cases a total of 135 blood cultures were found positive for candida species. Overall, 927 cases of cancer patients were found positive for any microorganisms while 2.1% (n=19) cases were found positive for candida specie. In every 100 cultures which were positive for any microorganism there were 2 cultures found to be positive for candida specie. The characteristics of study participants are summarized in Table 2.

No significant difference was observed across the three time periods. The type of cancers were categorized as solid or hematological for patients for whom data was available. Also, a decrease in proportion of *Candida albican* positive cultures was observed with the passage of time while the proportion of *C.tropicalis* positive cultures were reported. Although the proportion of *C.albican* positive culture was found to be constant across both solid and hematological cancers, but *C.tropicalis* was significantly more likely to be positive in hematological malignancies Table 3.

The investigation about treatment of patients and its outcomes were also made during hospitalization. Antifungal agents were administered to majority of the patients. Also, the mortality rate was significantly high during index hospitalization Table 4. The candidemia associated mortality rate was found to be higher in patients



**Table 2:** Characteristics of Study Population.

Characteristics	Jan-Feb (n = 51)	March-Apr (n = 39)	May - June (n = 45)	p-value	
	N (%)	N (%)	N (%)		
Age	<18 years	27 (52.9)	23 (58.9)	29 (64.4)	0.80
	18-59 years	13 (25.5)	13 (33.3)	12 (26.7)	
	≥60 years	11 (21.6)	3 (7.7)	4 (8.9)	
Gender	Male	31(60.8)	26 (66.7)	30 (66.7)	0.54
	Female	20 (39.2)	13 (33.3)	15 (33.3)	
Type of tumor	Hematological	29 (56.9)	21 (53.9)	24 (53.3)	0.76
	Solid	22 (43.1)	18 (46.2)	21 (46.7)	
Bacteremia	Yes	32 (62.7)	11 (28.2)	18 (40.0)	<0.01
	No	19 (37.2)	28 (71.8)	27 (60.0)	
Fever	Yes	48 (94.1)	36 (92.3)	40 (88.9)	0.41
	No	3 (5.9)	3 (7.7)	5 (11.1)	
Shock	Yes	17 (33.3)	12 (30.8)	9 (20.0)	0.14
	No	34 (66.7)	27 (69.2)	36 (80.0)	
Receiving Chemotherapy	Yes	43 (84.3)	32 (82.1)	35 (77.8)	0.77
	No	8 (15.7)	7 (17.9)	10 (22.2)	
Receiving TPN	Yes	7 (13.7)	3 (7.7)	4 (8.9)	0.16
	No	44 (86.3)	36 (92.3)	41 (91.1)	
Receiving Steroid	Yes	28 (54.9)	18 (46.2)	17 (37.8)	0.03
	No	23 (45.1)	21 (53.9)	28 (62.2)	
Had Central Venous Catheter	Yes	36 (70.6)	23 (58.9)	24 (53.3)	0.05
	No	15 (29.4)	16 (41.0)	21 (46.7)	
Received antibiotics in last 30 days	Yes	45 (88.2)	38 (97.4)	41 (91.1)	<0.01
	No	6 (11.8)	1 (2.6)	4 (8.9)	
Absolute neutrophil count	≤500	32 (62.7)	25 (64.1)	23 (51.1)	0.21
	>500	19 (37.3)	14 (35.9)	22 (48.9)	

**Table 3:** Types of Candida species isolated from study population (75.6%, n=102)

Patients N (%)	C.albican only N (%)	Non-candida albican only								Mixed			p-value
		C.tropicalis N (%)	C.prapsilosis N (%)	C.pelliculosa N (%)	C.glabrata N (%)	C.lusitaniae N (%)	C.famata N (%)	C.krusei N (%)	C.kefyr N (%)	C.albican & C.tropicalis N (%)	C.albican & C.parapsilosis N (%)	C.albican & C.glabrata N (%)	
Jan-Feb 24	11 (45.6)	8 (33.3)	1 (4.2)	1 (4.2)	--	--	--	--	--	2 (8.3)	1 (4.2)	--	<0.01
March-Apr 36	10 (27.8)	18 (50.0)	1 (2.8)	2 (5.6)	--	1 (2.8)	--	1 (2.8)	--	2 (5.6)	1 (2.8)	--	
May-June 42	8 (19.1)	19 (45.2)	4 (9.5)	1 (2.4)	2 (4.8)	1 (2.4)	2 (4.8)	1 (2.4)	1 (2.4)	2 (4.8)	--	1 (2.4)	
Solid tumors 46	13 (28.2)	17 (36.9)	4 (8.7)	2 (4.3)	3 (6.5)	2 (4.3)	1 (2.2)	1 (2.2)	--	2 (4.3)	1 (2.2)	--	<0.01
Hematological 56	16 (28.6)	23 (41.1)	4 (7.1)	2 (3.6)	--	3 (5.4)	1 (1.8)	1 (1.8)	1 (1.8)	3 (5.4)	1 (1.8)	1 (1.8)	

**Table 4:** Treatment and clinical outcomes among patients with Candidemia

Characteristics	Jan-Feb (n=51)	March-Apr (n=39)	May-June (n=45)	p-value	
	Duration of hospital stay (days)	Mean (Standard deviation)	12.4 (10.5)		13.8 (12.9)
	Range	0-43	0-62	0-109	
Received antifungal therapy	Yes	38 (74.5)	26 (66.7)	35 (77.8)	0.17
	Empirically	12	11	10	
	After positive culture	26	28	25	
Outcome	No	13 (25.5)	13 (33.3)	10 (22.2)	0.23
	Active	22 (43.1)	21 (53.4)	20 (44.4)	
	Dead	29 (56.9)	18 (46.2)	25 (55.6)	

with hematological malignancies (AOR: 2.1; 95% confidence interval [CI] 1.0-4.3) as compared to patients suffering from solid tumors. The mortality of patients positive for *C.albican* was significantly less (AOR 0.5; 95% CI = 0.1-0.7) as compared to those who were found positive for non-albican specie or a mixture of non-albican and albican species. The cancer patients who suffered from shock were at higher risk of candidemia associated mortality (AOR: 9.1; 95% CI = 4.1-19.3) as compared to those who were not in the state of shock. The patients who were not suffered from neutropenia were at significantly lower risk of candidemia associated mortality (AOR:

0.6; 95% CI = 0.1-1.1) as compared to neutropenic cancer patients. Furthermore, those patients who were administered with antifungal upon diagnosis were significantly at lower risk of dying with candidemia (AOR: 0.2; 95% CI = 0.1-0.6) as compared to those who did not administer an antifungal agent Table 5. The empiric therapy of antifungal agents before a positive blood culture was not significantly associated with higher rate of mortality ( $p < 0.05$ ).

## Discussion

The present study aimed to retrospectively analyze the medical records of cancer patients where the blood culture test was found positive for candida species among adult and pediatric populations. Findings revealed that per 100 cultures positive for any microorganism there were 2 cultures positive for *Candida* specie. Also, the disease burden of candidemia was not persistent throughout the study period. This is because *C.albican* was not only the common causative agent for candidemia. But in many cases non-albican species especially *C.tropicalis* was found positive for patients suffering from hematological malignancies. Among all the hospitalized cancer patients, the mortality rate of patients admitted in hospital for the first time was found in a range of 46%-57%. The study predicted the statistically significant association of factors with the higher rate of mortality and these include malignancy of hematological origin, positive blood culture test for non-albican species, absolute neutropenia (neutrophil count < 500), and not receiving timely antifungal agents.

Our findings revealed the outcome of adults and pediatric cancer patients suffering from hematological and solid tumors. Previously published studies in Pakistan were conducted on pediatric cancer patients suffering from [8], non-cancer patients [9-11] and immunocompromised patients who underwent stem cell transplantation [12]. The result of present study revealed that *C.albican* associated infections were found to be significantly less common than that of non-albican species especially *C.tropicalis*. From January to June most of the blood culture tests were found positive for *C.tropicalis*. Similar results have been reported in other studies among cancer patients [13,14]. This might be because of the fact that fluconazole was administered prophylactically to these patients especially sufferers of hematological malignancies. The efficacy of fluconazole was more against *C.albican* as compared to non-albican species. The increased use of this drug could be the reason of decline in *C.albican* associated infections. Also, the prevalence of non-albican species e.g., *C.tropicalis* is more in tropical and subtropical countries like Pakistan [15].

**Table 5:** Factors associated with risk of death during index hospitalization

Predictors		Bivariate analysis		Multivariate analysis	
		OR	95% CI	AOR	95% CI
Time period (compared to Jan-Feb)	March-Apr	0.5	0.3-1.0	0.6	0.2-1.3
	May-June	0.8	0.4-1.4	1.5	0.7-3.0
Age group (Compared to ages 18-59 years)	<18 years	0.5	0.2-0.7	0.5	0.1-1.0
	≥60 years	0.8	0.3-2.5	1.6	0.3-6.2
Males (Compared to females)		0.8	0.5-1.4	1.0	0.5-1.8
Hematological malignancy (Compared to solid tumors)		1.6	1.0-2.6	2.1*	1.0-4.3
Candida albican (Compared to non-C. albican or mixed)		0.6	0.3-1.0	0.5*	0.1-0.7
Bacteremia		1.6*	1.0-2.5	1.3	0.6-2.2
Shock		9.5**	4.7-17.6	9.1**	4.1-19.3
Receiving chemotherapy		0.8	0.5-1.7	1.2	0.4-3.5
Receiving TPN		1.8	0.7-3.6	2.6	0.7-8.0
Receiving steroids		1.0	0.5-1.6	0.5	0.2-1.0
ANC 500 or more (Compared to less than 500)		0.6	0.3-0.8	0.6*	0.1-1.1
Duration of stay in hospital		0.9	0.8-0.9	0.8	0.7-1.0
Receiving Amphotericin B (Compared to those not receiving)	Empirically	0.6	0.3-1.3	0.3	0.1-1.1
	After positive culture	0.2**	0.1-0.4	0.2**	0.1-0.6

OR: Odd Ratio, AOR: Adjusted Odd Ratio, CI: Confidence interval. TPN: Total Parenteral Nutrition. ANC: Absolute Neutrophil Count. \*: Significant at  $p=0.05$ ; \*\*: Significant at  $p=0.01$ .

Our findings revealed the mortality rate associated with candida species in between 46% and 57%. The high rate of mortality associated with candida species was also found by previously published systematic reviews of matched case-control studies. Likewise, other studies also predicted the mortality rate of cancer patients due to candida species between 50% and 61% [1,3]. But a Portuguese study found a significantly lower rate of candida associated mortality among cancer patients i.e., 31.9% [13].

The results of present study found non-albican species, shock, neutropenia and hematological malignancies as the significantly associated factors responsible for higher rate of mortality among cancer patients. Similarly, our this finding *C.tropicalis* was the most commonly found organisms in the blood samples of cancer patients is in line with the results of the study reported by Pfaller et al., [16]. Other studies also found hematological malignancies and neutropenia as the significantly associated risk factors for higher rate of mortality [14,17].

The multivariate analysis revealed that antifungal agents should be used when blood culture test found positive. In this study most of the patients with candidemia were administered with amphotericin B while some of the patients either died before the availability of blood culture test report or received fluconazole for *C.albican*. Most of the patients received amphotericin B, after the diagnosis of candidemia. Hence, it is recommended that all the cancer patients must be screened for candidemia. Also the prompt use of antifungal agents in these populations must be ensured to decrease the risk of mortality associated with candidemia.

### Strengths and limitations

As there is limited availability of previously published literature on the risk factors of candida associated mortalities among cancer patients especially in LMICs like Pakistan, so our results will be beneficial in understanding the epidemiology, management and outcome of candidemia in cancer patients from this part of the world. Antifungal agents are not used commonly because of their out of pocket cost but our findings suggest benefits of antifungal agents among cancer patients suffering from candidemia. So, this study emphasize the need of availability of antifungal drugs at lower cost. Like other studies it also has some limitations. First the data were uneven and retrospective in nature. The investigators stratify by time because of unevenness of data. Second, in some cases data related to candida specie were missing. This is because of the fact that blood culture test reports were not available during the study period. . But the investigators did not find any systematic differences across time periods because sample size and the length of study period is relatively short. Third, the investigators did not evaluate the mortality attributable to candidemia, rather all-cause mortality were evaluated. Fourth, the results cannot be generalized to all over the country because the study was conducted at a single healthcare setting. Fifth, the use of antifungal agents as a prophylaxis therapy was also not assessed. Lastly, as the minimum inhibitory concentrations and antifungal susceptibility were not assessed, so the resistance pattern of candida species against antifungal agents can't be evaluated.

### Conclusion

The blood culture tests of cancer patients were found to be positive for different species candida and bacteria simultaneously. There was no statistically significant risk factor found to be associated with candidemia. But the possible predictors during index hospitalization were hematological malignancies, shock and non-albican species of *Candida*.

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