ORIGINAL ARTICLE

Clinical features and outcomes of Candidaemia in cancer patients: Results from Pakistan

Aun Raza,[1] Waleed Zafar,[2] Amjad Mahboob,[3] Summiya Nizammudin,[4] Naveed Rashid,[5] Faisal Sultan[6]

Abstract

Objective: To evaluate clinical risk factors and outcomes among cancer patients with candidaemia at a large cancer treatment centre.

Methods: The retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data related to all cancer patients with a positive blood culture for candida species between January 1995 and December 2013

Results: A total of 311 patients were identified and there were 16 positive candida cultures among every 1000 (1.6%) cultures positive for any microorganism. Patients with haematological malignancies (adjusted odds ratio:2.23), those in shock (adjusted odds ratio: 9.48) were significantly more likely to die during the index hospitalisation, while patients with candida albicans isolated from the blood culture (adjusted odds ratio: 0.47) and those who received antifungal agent based on the sensitivity report of the fungal culture (adjusted odds ratio:0.32) were significantly less likely to die. Receipt of antifungal agents on an empirical basis before a positive culture was not significantly associated with mortality ($p>0.05$).

Conclusions: No statistically significant risk factor for candidemia was identified, but haematological malignancies, shock and candidaemia due to non-albicans species were predictors of mortality during index hospitalisation.

Keywords: Cancer patients, Candidaemia, Pakistan. (JPMA 66: 584; 2016)

Introduction

Fungal bloodstream infections (BSI) are an important risk factor for premature mortality among hospitalised cancer patients.[1] Candida BSI are one of the most common nosocomial infections. Candida infections among cancer patients have been associated with a crude mortality rate as high as around 50%.[1] Studies have indicated that the attributable mortality of candidaemia among hospitalised cancer patients is between 10% and 50%.[2,3] Candida BSI are also associated with much higher morbidity, longer duration of hospital stay, longer stay in the intensive care units (ICU) and more expensive care.[4]

While candida albican continues to be the most common pathogen isolated from immune competent patients' blood cultures, increasingly non-albican candida infections have been reported among cancer patients.[5] However, to date limited data has been reported regarding the epidemiology of candida BSI among cancer patients in the low- and middle-income countries (LMICs). Cancer patients in LMICs may be at a higher risk of candidaemia because of a generally poorer nutritional status at baseline, a later stage at diagnosis, and possibly greater challenges to adequate infection control.[6] As the number of cancer patients rises in LMICs, candidaemia is going to assume an increasing importance as a major cause of morbidity and mortality among these patients. Hence, the current study was planned to report the clinical risk factors and outcomes among cancer patients with candidaemia at a single cancer specialist centre in Pakistan.

Materials and Methods

The retrospective descriptive study was conducted at Shaukat Khanum Memorial Cancer Hospital & Research Centre (SKMCH&RC), Lahore, Pakistan, and comprised data related to all cancer patients with a positive blood culture for candida species between January 1995 and December 2013. The hospital is a 187-bed non-profit tertiary-care specialist cancer hospital with a referral base from all over the country and adjoining regions. In 2014, the hospital saw over 185,018 outpatient visits, 10,654 admissions, 8,352 surgical operations, 39,044 chemotherapy visits, and 56,444 radiation treatments.[7] Patient medical records at the hospital are completely electronic, and databases can be searched using key words or International Classification of Diseases versions 9 or 10 (ICD-9 / ICD-10) codes.

Using a structured data extraction form, we abstracted

[1,6]Department of Internal Medicine, [2]Section of Clinical Research, [4]Department of Pathology, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, [3]Department of Internal Medicine, Bacha Khan Medical Complex, Swabi, [5]Department of Internal Medicine, Rashid Latif Medical College, Lahore, Pakistan.

Correspondence: Aun Raza. Email: dr.aunraza@gmail.com

patients' demographic data and clinical information, including the infecting candida species, the underlying malignancy, symptoms and signs, use of parenteral nutrition, steroids (any dose and type in the preceding three months), central venous catheters, antibiotics, and chemotherapeutic agents (in the preceding three months), neutropenia status, and outcomes of hospitalisation. Separate episodes of hospitalisation and positive candida blood culture at different occasions were treated as separate episodes for the same patient. Since the hospital's medical records have been fully electronic only since 2006, we grouped the years before 2006 into one category after the study was approved by the institutional review board.

Bacteraemia was defined as presence of viable bacteria in blood culture concurrent with candidaemia. Candidaemia was defined as presence of candida species in a single blood culture. Duration of stay was taken as duration from the first day when a blood culture grew candida species till the day of discharge from the hospital or death, whichever was first. Shock was defined as systolic blood pressure <90mmHg, diastolic blood pressure <60mmHg and / or patient needing inotropic support to maintain blood pressure.

Detection of candidaemia and species identification of isolates was performed in the hospital's microbiology laboratory. Between 1995 and 2001, all blood samples were processed by the conventional manual blood culture system and all yeast isolated were identified and reported according to standard microbiological techniques. Yeast isolates were further analysed through the germ tube test and reported as candida albicans or candida non-albicans. From 2001 until 2007, BACTEC 9050 system (Becton Dickinson, USA) was used. This was followed by BACTEC 9240 system (Becton Dickinson, USA) in 2007 which is still currently in use. In 2006, API 20 C AUX (bioMérieux, France) was introduced for species identification and results were reported accordingly in concordance with the germ tube test results. During the study period, the anti-fungal agents available at our centre were Amphotericin B deoxycholate and fluconazole. Voriconazole became available only in 2005, while an echinocandin (Caspofungin) became available in 2006. However, the availability of the latter two drugs has been intermittent.

Standard descriptive summary statistics were used to characterise the sample of patients. Chi-square and Fisher's exact tests were used to compare categorical variables as appropriate. Multivariate logistic regression analyses were used to test the association of clinical characteristics with the primary outcome 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. Statistical analyses were performed using Stata version 12.

Results

A total of 311 blood cultures positive for candida species were identified. The total number of blood cultures of cancer patients positive for any microorganism was 12,215 and positive for candida species was 195(1.6%), yielding 16 positive Candida cultures among every 1000 (1.6%) cultures positive for any microorganism (Figure). Demographic and clinical characteristics of the patients were noted (Table-1). There were no significant variations across the three time periods and it was assessed whether the tumour was solid or haematological for patients for whom data was available. It was seen that over time, the proportion of cultures positive for C. albicans declined, while the proportion for non-albicans species has gone up particularly for C.tropicalis. Similarly, while the proportion of cultures positive for C. albicans is constant across haematological and solid malignancies, C.tropicalis was

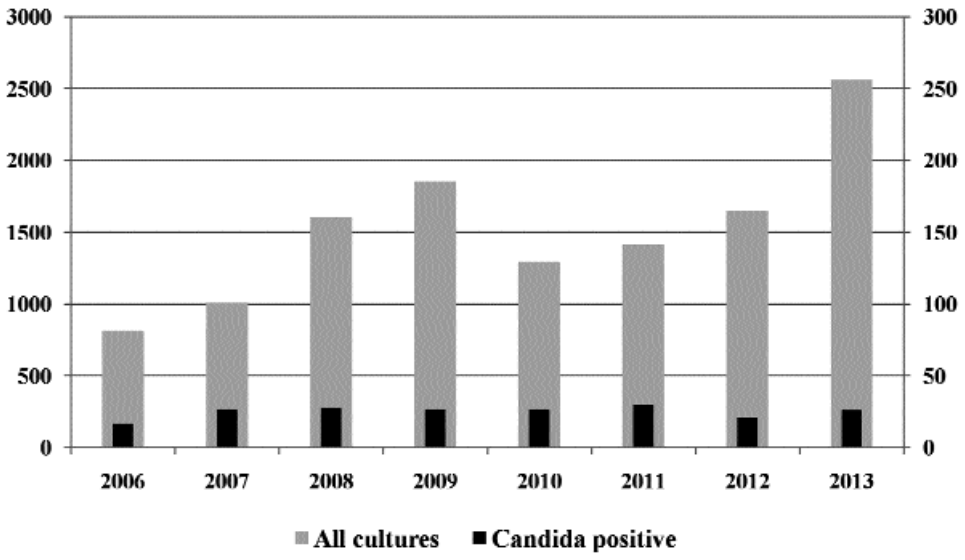

Figure: Total number of all positive cultures for any microorganism (left axis) and for Candida species (right axis) among cancer patients per year between 2006 and 2013.

Table-1: Demographic and baseline clinical characteristics of patients.

Characteristic	Before 2006 N=116		2006-2009 N=93		2010-2013 N=102		p
	N	%	N	%	N	%	
Age in years							
Less than 18	68	58.6	55	59.1	67	65.7	0.81
18-59	39	33.6	32	34.4	28	27.4	
60 or older	9	7.8	6	6.4	7	6.9	
Gender							
Male	70	60.3	61	65.6	69	67.6	0.51
Female	46	39.7	32	34.4	33	32.3	
Type of tumour							
Haematological	68	58.6	51	54.8	55	53.9	0.77
Solid	48	41.4	42	45.2	47	46.1	
Bacteraemia							
Yes	73	62.9	27	29.0	41	40.2	<0.01
No	43	37.1	66	71.0	61	59.8	
Fever[1]							
Yes	109	94.0	86	92.5	91	89.2	0.42
No	7	6.0	7	7.5	11	10.8	
Shock[1]							
Yes	39	33.6	28	30.1	22	21.6	0.13
No	77	66.4	65	69.9	80	78.4	
Receiving chemotherapy[1]							
Yes	97	83.6	77	82.8	81	79.4	0.72
No	19	16.4	16	17.2	21	20.6	
Receiving total parenteral nutrition							
Yes	17	14.7	7	7.5	9	8.8	0.19
No	99	85.3	86	92.5	93	91.2	
Receiving steroids							
Yes	64	55.2	44	47.3	39	38.2	0.04
No	52	44.8	49	52.7	63	61.8	
Had central venous catheter							
Yes	81	69.8	56	60.2	55	53.9	0.05
No	35	30.2	37	39.8	47	46.1	
Received antibiotics in last 30 days							
Yes	102	87.9	92	98.9	92	90.2	<0.01
No	14	12.1	1	1.1	10	9.8	
Absolute neutrophil count							
500 or less	73	62.9	59	63.4	54	52.9	0.23
More than 500	43	37.1	34	36.6	48	47.1	

[1]At the time of sample collection.

significantly more likely to be positive in haematological than in solid organ malignancies (Table-2).

The treatment patients received in the hospital and the outcome of the stay was also noted. Most patients received an antifungal agent. Nonetheless, mortality during the index hospitalisation among cancer patients with Candidaemia was high (Table-3).

Patients with haematological malignancies were significantly more likely to die of candidaemia (AOR: 2.23; 95% confidence interval [CI]1.11-4.51) compared to patients with solid tumours. Patients with C. albicans isolated from the blood culture were significantly less likely (AOR 0.47; 95% CI 0.23-0.95) to die compared with patients with non-albicans or a mixture of albicans and non-albicans species. Patients who were in shock at the time of sample collection were at a much higher risk of death (AOR 9.48; 95% CI 4.59-19.6) compared to patients who were not in shock. Patients with absolute neutrophil count of 500 or more were significantly less likely (AOR 0.45; 95% CI 0.24-1.00) to die compared to patients with a neutrophil count of less than 500. Patients who received

Table-2: Types of candida species isolated among cancer patients (n=236).

		Non- C. albicans only									Mixed			
		C. albicans only	C.tropicalis	C.prapsilosis	C.pelliculosa	C.glabrata	C.lusitaniae	C.famata	C.krusei	C.kefyr	C.albicans & C.tropicalis	C.albicans & C.parapsilosis	C.albicans & C.glabrata	p
Before 2006	N	23	19	1	3	-	-	-	-	-	4	1	-	
	%	45.1	37.2	2.0	5.9	-	-	-	-	-	7.8	2.0	-	
2006-2009	N	27	44	3	5	-	1	-	1	-	2	1	-	<0.01
	%	32.1	52.4	3.6	5.9	-	1.2	-	1.2	-	2.4	1.2	-	
2010-2013	N	21	52	10	1	6	1	2	1	1	2	-	1	
	%	20.8	51.5	9.9	1.0	5.9	1.0	2.0	1.0	1.0	2.0	-	1.0	
Solid tumors	N	32	42	10	7	6	2	1	1	-	5	1	-	
	%	29.9	39.2	9.3	6.5	5.6	1.9	0.9	0.9	-	4.7	0.9	-	<0.01
Haematological	N	39	73	4	2	-	3	1	1	1	3	1	1	
	%	30.2	56.6	3.1	1.5	-	2.3	0.8	0.8	0.8	2.3	0.8	0.8	

C: Candida.

Table-3: Treatment and clinical outcomes among patients with Candidaemia.

	Before 2006 N=116		2006-2009 N=93		2010-2013 N=102		p
Characteristic							
Duration of stay in hospital (days)							
Mean (Standard deviation)	13.5	(11.5)	14.9	(13.9)	20.8	(19.2)	<0.01
Range	0-54		0-73		0-120		
	N	**%**	**N**	**%**	**N**	**%**	
Received antifungal therapy							
Yes	86	74.1	62	66.7	80	78.4	0.18
Empirically	31		15		17		
After positive culture	55		47		63		
No	30	25.9	31	33.3	22	21.6	
Outcome							
Alive	49	42.2	50	53.8	46	45.1	0.24
Dead	67	57.8	43	46.2	56	54.9	

Table-4: Factors associated with risk of death during index hospitalisation.

Predictors	Bivariate analysis		Multivariate analysis	
	Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
Time period (compared to 1996-2005)				
2006-2009	0.63	0.36-1.09	0.70	0.34-1.41
2010-2013	0.89	0.52-1.52	1.57	0.79-3.13
Age group (Compared to ages 18-59 years)				
Younger than 18 years	0.50	0.30-0.84	0.51	0.24-1.10
60 years or older	0.99	0.38-2.61	1.74	0.47-6.50
Males (Compared to females)	0.96	0.60-1.53	1.11	0.63-1.97
Haematological malignancy (Compared to solid tumours)	1.70	1.08-2.68	2.23*	1.11-4.51
Candida albicans (Compared to non-C. albicans or mixed)	0.65	0.38-1.10	0.47*	0.23-0.95
Bacteraemia	1.67*	1.06-2.62	1.42	0.79-2.54
Shock	9.59**	4.93-18.7	9.48**	4.59-19.6
Receiving chemotherapy	0.99	0.55-1.77	1.40	0.53-3.68
Receiving TPN	1.86	0.87-3.99	2.78	0.96-8.05
Receiving steroids	1.08	0.69-1.69	0.64	0.35-1.12
ANC 500 or more (Compared to less than 500)	0.66	0.42-1.04	0.49*	0.24-1.00
Duration of stay in hospital	1.00	0.99-1.02	0.99	0.97-1.01
Receiving Amphotericin B (Compared to those not receiving)				
Empirically	0.70	0.35-1.40	0.44	0.18-1.12
After positive culture	0.31**	0.18-0.54	0.32**	0.15-0.69

CI: Confidence interval. TPN: Total Parenteral Nutrition. ANC: Absolute Neutrophil Count. *: Significant at p=0.05; **: Significant at p=0.01.

antifungal agent-based on the sensitivity report of the fungal culture were significantly less likely to die (AOR 0.32; 95% CI 0.15-0.69) compared to patients who did not receive an antifungal agent (Table-4). Receipt of antifungal agents on an empirical basis before a positive culture was not significantly associated with mortality ($p<0.05$).

Discussion

The aim of this study was to retrospectively review patient records in all cases where a blood culture was positive for candida species among adult and paediatric hospitalised cancer patients at a tertiary care cancer specialist centre in Pakistan over a period of 19 years. We found that there were 16 positive candida cultures among every 1000 cultures positive for any microorganism. We also deduced that over time there was a significant change in the epidemiology of candidaemia among cancer patients. C.albicans is no longer the most commonly isolated species. Instead, non-albican species, particularly C.tropicalis was leading the list by being isolated from a majority of cultures, especially from patients with haematological malignancies. Mortality among hospitalised cancer patients with candidaemia during the index hospitalisation was very high ranging from 46% to 58%. Having haematological malignancy or non-albicans candida species, being in shock, having an absolute neutrophil count of less than 500, and not receiving timely antifungal agents were significantly associated with higher risk of mortality.

To our knowledge, this is the first study from Pakistan to report outcomes among cancer patients with candidaemia that reports data for paediatric and adult patients as well as for haematological and solid tumours. Prior studies from Pakistan were conducted on paediatric patients with cancer who developed healthcare associated infections, including candidaemia,[8] patients who did not have cancer[9-11] and patients with stem cell transplantation.[12]

In our study there was a gradual decline in C.albicans isolates and a significant rise in the detection of non-albicans candida species, particularly C.tropicalis. The proportion of C.tropicalis isolated from the positive cultures increased from 37% before 2006 to 51.5% between 2010 and 2013. Similar results have been reported in other studies among cancer patients.[13,14] A possible reason for this shift is the use of fluconazole prophylactically in cancer patients, particularly in those with haematological malignancies. Since fluconazole is more efficacious against C.albicans than against non-albicans candida species,its increased use could explain this shift in candida epidemiology. Moreover, C.tropicalis is more prevalent in tropical and subtropical countries like Pakistan.[15]

The mortality rate in our sample was between 46% and 58%. Systematic reviews of matched case-control studies have found attributable mortality rate of candidaemia to be high as well. Our results are in line with the previous studies where crude mortality was found to be between 50% and 61%.[1,3] However, this range is significantly higher than a Portuguese study that found mortality in cancer patients due to candidaemia to be 31.9%.[13]

The study also allowed us to identify that shock, non-albicans candidaemia, neutropenia and haematological malignancies were predictors of mortality among hospitalised cancer patients with candidaemia. Pfaller et al. had also previously reported similar findings in their study with C.tropicalis being the cause of highest mortality in their patients.[16] Similarly, haematological malignancies and neutropenia have also been associated with increased mortality.[14,17] Of the 311 patients with candidaemia in this study, 73% received amphotericin B, while the rest of the patients received either fluconazole for c.albicans or died before the culture report was available for candida BSI. Unfortunately, we were unable to review the exact number of these patients. Out of 228 patients who received amphotericin B, 72% received it after positive culture report for candida species. Our study favours the use of antifungal agents after a positive culture report which is shown in multivariate analysis.

There were few strengths of this study. Firstly, we had a large sample size over a long period. Secondly, no data like this has been reported from Pakistan or most developing countries where newer antifungals are too expensive to be used routinely so this data will prove to be beneficial in understanding the epidemiology, management and outcome of candidaemia in cancer patients from this part of the world.

There were several limitations of the study as well. Firstly, this was a retrospective study with uneven data, but most candidaemia studies are retrospective in nature. We present data over a long time. We stratify by time to take the unevenness of data into account. Secondly, we have missing data for candida species (n=236 versus 311 for total sample). Most of this missing data was pre-2006 when we had different diagnostic techniques. We could do nothing about this. We found no systematic differences across time periods. Thirdly, we did not assess the mortality attributable to candidaemia, rather we evaluated for all-cause mortality. Fourthly, the study was conducted at a single institution so its results cannot be generalised. Fifthly, we did not look for what antifungals were given as prophylaxis to these

patients. Lastly, since anti-fungal susceptibilities and minimum inhibitory concentrations were not checked for these isolates, we cannot comment on the resistance pattern of candida to different antifungals.

Conclusions

Simultaneous bacteraemia and candidaemia with different species was not uncommon in cancer patients. No statistically significant risk factor for candidaemia was identified. However, haematological malignancies, shock and candidaemia due to non-albicans species were predictors of mortality during index hospitalisation.

Acknowledgments

We are grateful to Dr. Khawaja Farhan Zahid for assistance in data extraction.

References

1. Tang HJ, Liu WL, Lin HL, Lai CC. Epidemiology and prognostic factors of Candidemia in cancer patients. PLoS One 2014; 9: e99103.
2. Falagas ME, Apostolou KE, Pappas VD. Attributable mortality of candidemia: a systematic review of matched cohort and case-control studies. Eur J Clin Microbiol Infect Dis 2006; 25: 419-25.
3. Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 2003; 37: 1172-7.
4. Taur Y, Cohen N, Dubnow S, Paskovaty A, Seo SK. Effect of antifungal therapy timing on mortality in cancer patients with Candidemia. Antimicrob Agents Chemother 2010; 54: 184-90.
5. Hachem R, Hanna H, Kontoyiannis D, Jiang Y, Raad I. The changing epidemiology of invasive Candidiasis: Candida glabrata and Candida krusei as the leading causes of Candidemia in hematologic malignancy. Cancer 2008; 112: 2493-9.
6. Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, et al. Time to initiation of fluconazole therapy impacts mortality in patients with Candidemia: A multi-institutional study. Clin Infect Dis. 2006; 43: 25-31.
7. Sultan F, Aziz MT, Khokhar I, Qadri H, Abbas M, Mukhtar A, et al. Development of an in-house hospital information system in a hospital in Pakistan. Int J Med Inform 2014; 83: 180-8.
8. Siddiqui NU, Wali R, Haque AU, Fadoo Z. Healthcare-associated infections among pediatric oncology patients in Pakistan: risk factors and outcome. J Infect Dev Ctries 2012; 6: 416-21.
9. Ariff S, Saleem AF, Soofi SB, Sajjad R. Clinical spectrum and outcomes of neonatal candidiasis in a tertiary care hospital in Karachi. Pak J Infect Dev Ctries. 2011; 5: 216-23.
10. Bhatti MA, Karmarkar R, Wagner DK. Candida albicans myocardial abscess. J Coll Physicians Surg Pak 2003; 13: 456-8.
11. Kumar S, Kalam K, Ali S, Siddiqi S, Baqi S. Frequency, clinical presentation and microbiological spectrum of candidemia in a tertiary care center in Karachi, Pakistan. J Pak Med Assoc 2014; 64: 281-5.
12. Ullah K, Ahmed P, Raza S, Satti T, Nisa Q, Mirza S, et al. Allogeneic stem cell transplantation in hematological disorders: single center experience from Pakistan. Transplant Proc 2007; 39: 3347-57.
13. Sabino R, Verissimo C, Brandao J, Alves C, Parada H, Rosado L, et al. Epidemiology of Candidemia in oncology patients: a 6-year survey in a Portuguese central hospital. Med Mycol 2010; 48: 346-54.
14. Ma CF, Li FQ, Shi LN, Hu YA, Wang Y, Huang M, et al. Surveillance study of species distribution, antifungal susceptibility and mortality of nosocomial candidemia in a tertiary care hospital in China. BMC Infect Dis 2013; 13: 337.
15. Chai LYA, Denning DW, Warn P. Candida tropicalisin human disease. Crit Rev Microbiol 2010; 36: 282-98.
16. Pfaller MA, Andes DR, Diekema DJ, Horn DL, Reboli AC, Rotstein C, et al. Epidemiology and outcomes of invasive candidiasis due to non-albicans species of Candida in 2,496 patients: Data from the Prospective Antifungal Therapy (PATH) registry 2004-2008. PLOS One 2014; 9: e101510.
17. Bassetti M, Merelli M, Righi E, Diaz-Martin A, Rosello EM, Luzzati R, et al. Epidemiology, species distribution, antifungal susceptibility, and outcome of Candidemia across five sites in Italy and Spain. J Clin Microbiol 2013; 51: 4167-72.