Epidemiology and Outcomes of Candidaemia among Adult Patients Admitted at Hospital Universiti Sains Malaysia (HUSM): A 5-Year Review

Haydar A[a]
[a]*Department of Internal Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, 25200 Kuantan, Pahang*

ABSTRACT

Introduction: *Candida* organisms are opportunistic fungal pathogens that have become a major cause of nosocomial infections worldwide. We investigated the clinical characteristics and outcomes of hospitalized patients with candidaemia caused by *Candida albicans* and non-*albicans Candida spp* at HUSM. **Materials and Methods:** We retrospectively evaluated all hospitalized patients with candidaemia from January 2010 till December 2014 based on inpatient hospital records and laboratory data. **Results:** A total of 134 patients with candidaemia were enrolled. *Candida albicans* and non-*albicans Candida spp* were responsible for 20% (27/134) and 80% (107/134) of candidaemia cases, respectively. Hospitalized patients with diabetes mellitus, surgical conditions, or concomitant septicaemia and those who received instrumentations such as CVC or CBD, and those admitted under medical settings were prone to develop candidaemia caused by either *C. albicans* or non-*albicans Candida spp*. All isolates were susceptible to Fluconazole except for *C. krusei* isolates. All-cause mortality within 30 days post diagnosis of candidaemia was 59%. Factors associated with mortality were solid tumor (p =0.014), surgical illness (p=0.128), central venous catheterization (p= 0.096) and leucocytosis (p=0.116). Only solid tumor was an independent contributory factor for mortality among patients with *C. albicans* candidaemia in the multivariate analyses (OR 5.09, 95% CI 1.38,18.74, p=0.014). **Conclusions:** The patients' clinical characteristics were fairly comparable between *Candida albicans* and non-*albicans* candidaemia. The changing epidemiology of candidaemia at this centre was in fact alarming. The outcome associated with candidaemia was poor.

KEYWORDS: Candidaemia, *Candida albicans*, non-*albicans*

INTRODUCTION

The incidence of candidaemia is increasing significantly in recent years. It was the fourth most common cause of bloodstream infections (BSI) at United States hospitals[1] and the leading cause of nosocomial BSI at some hospitals in Taiwan.[2] In the past, almost all *Candida* isolates responsible for bloodstream infections were *Candida albicans*. Whereas in recent years, a growing proportion of episodes of candidaemia have been caused by *Candida* species other than *albicans*. Non-*albicans* candidaemia (NAC) has been shown to be responsible for 36-63% of all candidaemia cases.[2] The most common non-*albicans* species are *Candida parapsilosis* and *Candida glabrata*, followed by *Candida tropicalis* and *Candida krusei*, and their incidence varies among institution and different geographical regions.[3] Although *Candida* species are opportunistic pathogens, the majority of patients who develop disseminated candidiasis are not immunosuppressed. Rather, the predominant risk factors for disseminating candidiasis are common iatrogenic or nosocomial factors. Clinical presentation of candidaemia may span from the absence of specific symptoms to severe sepsis or septic shock. Candidaemia remains associated with high crude and attributable mortality rates and with increased costs of care and duration of hospitalization.[4] Therefore, the knowledge of local epidemiology of *Candida* infections is important in order to offer sound management of invasive candidiasis. In the present study, we compared the clinical characteristics, treatment and outcomes of patients with *Candida albicans* candidaemia and NAC.

Corresponding author:
Dr Amalina Haydar Ali Tajuddin
Department of Internal Medicine
Kulliyyah of Medicine,
International Islamic University Malaysia (IIUM)
25200, Kuantan, Pahang, Malaysia
Email : ahataj@yahoo.com
Phone no : +60133539557

MATERIALS AND METHODS

Patient enrollment and data collection

We retrospectively evaluated the medical and microbiological data on all cases of candidaemia in HUSM from January 2010 till December 2014. Demographic data, comorbidities, microbiological data and patients' outcomes were analyzed. The inclusion criteria comprised of all adult patients (age≥18 years old) with at least one positive blood culture yielding *Candida* spp. Patients with candidaemia caused by one than one species in one blood culture were excluded. Cases were categorized

according to first or recurrent episodes of candidaemia within the study period. Case was categorized as breakthrough candidaemia if the patient had received systemic antifungal therapy for any reason ≥ 5 days before the first positive blood culture.[5]

Mycological studies

Laboratory information included full blood count, blood culture and sensitivity reports and MIC values from antifungal susceptibility testing. Blood culture technique was based on standardized protocol. Blood cultures were ordered at the discretion of the primary physician because of signs and symptoms of possible invasive fungal infections. Trained medical personnel obtained all blood samples by using sterile technique. All blood samples were processed in the Microbiology Laboratory at HUSM.

The diagnostic laboratory was equipped with automated blood culture systems. Speciation of *Candida sp* was done using biochemical tests, sugar assimilation, germ tubes test, incubation at 45^0C (to differentiate *C. dubliniensis and C. albicans*), cornmeal tween agar and also commercialized identification system, API-32C system (bioMerieux,Inc, St. Louis, MI). Antifungal susceptibility testings to Amphotericin B, Caspofungin, Fluconazole and Voriconazole were performed by using the Etest method. MIC results were interpreted according to species-specific clinical breakpoints as established by the Clinical and Laboratory Standards Institute (CLSI) for Amphotericin B, Caspofungin, Fluconazole and Voriconazole.[6] At this hospital, the antifungal susceptibility testing results were only available in 105(78.4%) and 98(73.1%) candidaemia cases for Fluconazole/Amphotericin B and Voriconazole/ Caspofungin, respectively (depending on the availability of the reagents used at the time of blood culture).

Study Variables

Clinical characteristics of patients that were evaluated in this study included demographic profile, underlying illnesses, predisposing factors, antifungal therapy and outcomes within 30 days post diagnosis of candidaemia. All clinical data of 134 patients were recorded in standardized forms. Underlying illnesses, including diabetes mellitus, surgical conditions, solid tumor, hematological malignancy, dialysis dependent, and HIV infection were documented. Predisposing factors that occurred within 14 days prior to diagnosis of candidaemia were also collected. These included haemodynamic status, concomitant septicaemia, ongoing corticosteroid or immunosuppressive therapy, systemic microbial therapy, prior antifungal therapy, central venous catheterization, urinary catheterization, total parenteral nutrition and mechanical ventilation. Laboratory data (TWBC, ANC and platelet counts) within 7 days before obtaining the first positive blood culture positive were analyzed.

STATISTICS

Data were analyzed by using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The Chi-square test was used in the analyses of contingency tables whereas Fisher's exact test was employed if the sample size was small. The mean and standard deviation (SD) were used to describe numerical data. The independent T-test was used to compare means of continuous variables in normal distribution. Mann-Whitney test was used for skewed continuous data such as duration of antibiotics. The occurrence of death in candidaemia due to either *C. albicans* or non-*albicans Candida* species were treated as a dependent variable in both univariate and multivariate logistic regression analyses. Age, gender, underlying illnesses and predisposing factors were treated as independent categorical variables in univariate analyses. Potential factors were included in the multivariate analyses if they were associated with the dependent variable at a statistical level of $p<0.25$.

Multivariate logistic regression analyses were performed to identify independent variable associated with all-cause mortality within 30 days post diagnosis of candidaemia. Multiple associations were evaluated in the multiple logistic regression model based on backward stepwise selection. The adjusted measure of association between risk factors and the independent variable was expressed as the odds ratio (OR) with 95% confidence interval (95% CI). Adjusted or crude ORs with 95% CI that did not include 1.0 were considered significant. The odds ratio was computed as the odds of a patient having the factor and died due to *C. albicans* candidaemia, divided by the odds of patients having that and died due to non-*albicans* candidaemia A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

A total of 134 cases were analyzed in this section. Collectively, *Candida albicans* and non-*albicans Candida spp* were responsible for 20% (27/134) and 80% (107/134) for candidaemia cases, respectively. The distribution was as follows; *Candida parapsilosis* 25.4% (34/134), *Candida tropicalis* 24.6% (33/134), *Candida glabrata* 20.1% (27/134), *Candida albicans* 20.1% (27/134), *Candida krusei* 1.5% (2/134), *Candida guillermondii* 3.7% (5/134), *Candida rugosa* 1.5% (2/134), *Candida dubliniensis* 1.5% (2/134), and unspecified *Candida spp* 1.5% (2/134). All patients with *Candida albicans* were noted to have only first and single episode of candidaemia within the study duration. All 3 cases of recurrent candidaemia (either with similar *Candida spp* or different *Candida spp*) were caused by non-a*lbicans Candida spp*. Similarly, 7 out 9 cases of

breakthrough candidaemia recorded were also caused by NAC (77.8%).

For both groups of *C. albicans* and NAC, patients were likely to have the following risk factors; dialysis dependent, diabetes mellitus, surgical condition, received prolonged duration of systemic antimicrobial therapy and had medical instrumentations such as central venous catheterization and urinary catheterization.

A comparison of patients' clinical characteristics between those with candidaemia caused by *Candida albicans* versus NAC is shown in Table 1. Interestingly, patients with *C. albicans* isolates were found to a higher number of TWBC, than those with non-*albicans* infection (p = 0.003).

Moreover, non-*albicans* species were commonly isolated from patients with neutropenia (70%) and severe thrombocytopenia (85.7%). Half of the

Table 1 Patients' clinical characteristics grouped according to candidaemia caused by *C. albicans* and non-*albicans Candida spp*

Characteristics	All (n = 134)	*Candida* Species		p value
		Candida albicans (n=27)	NAC (n=107)	
Age (mean ± SD)	53.3 ± 16.8	53.7 ± 16.9	53.3 ± 16.9	0.918[d]
Sex				
Male	72 (53.7)	13 (48.1)	59 (55.1)	0.515[e]
Female	62 (46.3)	14 (51.9)	48(44.9)	
Race				
Malay	123 (91.8)	25 (92.6)	98(91.6)	0.143[e]
Chinese	7(5.2)	2(7.4)	5(4.7)	
Siamese	2(1.5)	-	2(1.9)	
Others	2(1.5)	-	2(1.9)	
Underlying illness/condition				
Diabetes mellitus	60(44.8)	12(44.4)	48(44.9)	0.969[e]
Surgical condition	60(44.8)	11(40.7)	49(45.8)	0.637[e]
Hematological malignancy	20(14.9)	5(18.5)	15(14.0)	0.553[c]
Solid tumor	22(16.4)	8(29.6)	14(13.1)	0.076[c]
Dialysis dependent	28(47.5)	4(36.4)	24(50.0)	0.414[e]
HIV infection	1(0.7)	-	1(0.9)	>0.999[c]
Predisposing factors[f]				
Hemodynamic status				
Stable	58(43.3)	12(44.4)	46(43.0)	0.892[e]
Septic shock	76(56.7)	15(55.6)	61(57.0)	
Central venous catheterization	116(86.6)	22(81.5)	94(87.9)	>0.361[c]
Urinary catheterization	126(94.0)	25(92.6)	101(94.4)	>0.662[c]
Total parenteral nutrition	45(33.6)	9(33.3)	36(33.6)	0.976[e]
Mechanical ventilation				
Invasive	62(46.3)	12(44.4)	50(46.7)	0.568[e]
Non invasive	2(1.5)	1(3.7)	1(0.9)	
Ongoing corticosteroid therapy	46(34.3)	10(37.0)	36(33.6)	0.740[e]
Ongoing immunosuppressive therapy	2(1.5)	-	2(1.9)	>0.999[e]
Ongoing chemotherapy	19(14.2)	4(14.8)	15(14.0)	>0.999[c]
Systemic antimicrobial therapy	114(85.1)	24(88.9)	90(84.1)	0.764[c]
Duration of antibiotic (days)[a]	12(19.0)	14(20.0)	12(19.0)	0.304[b]
Prior antifungal therapy	23(17.2)	3(11.1)	20 (18.7)	0.568[c]
Investigation profile				
WBC [a]	11.6(12.4)	15.8(13.3)	9.5(10.6)	0.003[b]
ANC count				
<1.00 x 10^9/L	20 (14.9)	6(22.2)	14(13.1)	0.237[c]
≥1.00 x 10^9/L	114(85.1)	21(77.8)	93(86.9)	
Platelet count				
<20000/mm^3	14(10.4)	2(7.4)	12(11.2)	0.358[e]
20000 to 100000/mm^3	42(31.3)	6(22.2)	36(33.6)	
>100000/mm^3	78(58.2)	19(70.4)	59(55.1)	

[a] Median(IQR)
[b] Mann-Whitney test
[c] Fisher Exact Test
[d] Independent T-test
[e] Pearson Chi-Square test
[f] Within 2 weeks before the initial positive culture result

patients had superimposed septicaemia and candidaemia, which was frequently complicated by septic shock (56.7%) and invasive mechanical ventilation (46.3%). In subgroup analyses, among those with underlying malignancy, candidaemia were more commonly caused by non-*albicans Candida* strains, which occurred in 63.6% of cases of solid tumor and 75% of hematological malignancy respectively.

Distribution of candidaemia cases, according to hospital wards is shown in Figure 1. 96 (71.6%) candidaemia cases received treatment with antifungal therapy during hospitalization. 22 out of 38 (57.9%) non-treated cases were due to death within 24 hours of blood culture collection and before detection of candidaemia. Only 22 patients (22.9%) were started on empirical antifungal therapy within 24 hours of blood culture taken. Time to initiation for antifungal therapy for the remaining 74 patients were as follows; day 1 (14.6%), day 2 (26%) and day 3 and above (36.4%).

However, time of antifungal initiation after 48 hours was found to be statistically insignificant (p=0.282) in our univariate analyses for fatal candidaemia cases at this center. In a subgroup analysis of timing for antifungal therapy, according to ward distribution, empirical antifungal was frequently started on the day of blood culture for majority of cases at ICU (36.8%). On the other hand, candidaemia cases from general medical wards (66.7%), medical HDW (55%) and general surgical wards (50%) revealed delayed antifungal initiation after 48 hours (day 3 onwards).

In general, Fluconazole and Caspofungin have been the most frequently administered in 51.1% and 39.1% of treated cases respectively. The *in vitro* susceptibilities of *Candida spp* to antifungal agents list in Table 2. A high overall mortality of 59% was observed among patients with candidaemia. Despite its lower occurrence, *C. albicans* candidaemia were found to have a higher number of mortality cases (63%) than NAC (57.9%). 27.8% (22 of 79) were due to deaths that occurred before the diagnoses of candidemia were made and effective treatment could be commenced.

The simple logistic regression analyses of factors associated with mortality are shown in Table 4. Females (52.9%) and slightly older patients were more likely to die from *Candida albicans* candidaemia, whereas patients with diabetes mellitus (51.6%), surgical conditions (56.5%) or dialysis dependent (56.7%) were more likely to die from NAC. Almost all of them were put on instrumentation with central venous catheterization (98.4%) and urinary catheterization (100%). 27.8% of death cases did not receive any antifungal therapy. The four independent variables whose univariable test p value less than 0.25 were selected for multivariable logistic regression, namely surgical conditions (p=0.128), solid tumor (p=0.014), central venous catheterization (p=0.096) and leukocytosis (p=0.114). After multivariate analyses, solid tumor was found to be an independent contributory factor in mortality caused by *C. albicans* candidaemia (OR 5.09, 95% CI 1.38,18.74, p=0.014).

DISCUSSION

Over the five year review, an apparent increment in the total number of non-*albicans* candidaemia (NAC) was observed. This is consistent with the findings in previous study done at HUSM, which showed a significant reduction in trend of *Candida albicans* isolates in blood and increment in the non-*albicans* isolates for the proportion of cases at this center within 2001 till 2006.[7] For comparison, data from Taiwan showed that the proportion of *Candida albicans* in patients with candidaemia decreased from 64.8% to 43.6% whereas the proportion of *Candida glabrata* increased greatly from 1.1% to 21.6%.[2] The proportion of NAC in our study is 25.4% for *C. parapsilosis*, 24.6% for *C. tropicalis* and 20.1%

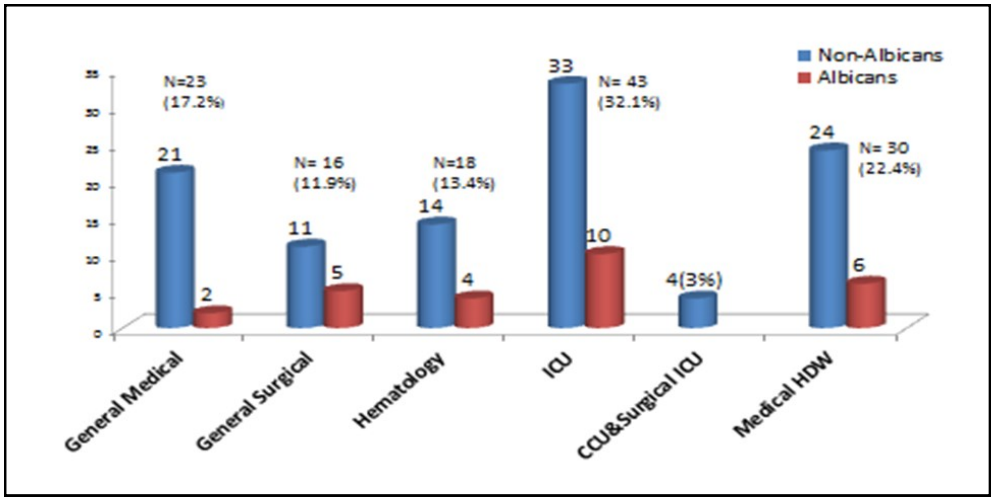

Figure 1 Distribution of candidaemia cases according to hospital ward
* General surgical included surgical ward, O&G, orthopaedic and ORL wards
* Surgical ICU included SICU, CRW and neurosurgery HDW

for *C. glabrata*. Our results are in accordance with previously published studies in Taiwan.[2,8]

Some clinical factors may consistently impact the risk of developing candidaemia due to non-*albicans Candida* species. For example, *C. parapsilosis* candidaemia has been associated with vascular catheters and parenteral nutrition, *C. tropicalis* candidaemia is associated with cancer and neutropenia and *C. krusei* and *C. glabrata* candidaemias are associated with previous exposure to azoles.[9] Other factors, such as prolonged exposure to antibiotics, ongoing immunosuppressive therapy, and the underlying medical condition of the host might as well affect the distribution of *Candida* species. Interesting differences emerged in the profiles of patients with candidaemia between our data and studies from other centers. Latin American and European studies have indicated that 56.5% and 44.4% of episodes of nosocomial candidaemia cases, respectively, occurred in patients in the ICU.[10] In contrast, our study revealed that a large proportion (39.6%) of *Candida spp* isolates from blood culture were collected from patients under internal medicine settings (general medical wards and high dependency ward), if compared to total proportion of cases from ICU (32%).

Our data were comparable to a study of 209 candidaemia cases in Taiwan that revealed more patients (69.8%) were admitted to the medical units.[8] Majority (33.6%) of NAC cases were also encountered under internal medicine settings. In another study by M. Bassettii,[11] which specifically addressed the epidemiological aspects of candidaemia in the internal medicine wards, had revealed similar variables associated with internal medicine wards candidaemia as observed in this study. These include urinary or central venous catheter, parenteral nutrition, tumors and delayed administration of antifungal treatment (48 h after having the first positive blood culture).

Our study discovered that candidaemia occurred in only 14.9% of patients with hematological malignancies. Based on the SEIFEM-2004 study, patients with hematologic malignancies are currently at higher risk of invasive fungal infections caused by molds (2.9%) rather than by yeasts (1.6%).[12] *Aspergillus* spp (2.6%) are still the most common pathogens, followed by *Candida* spp (1.5%). This might explain on the low proportion of candidaemia cases among patients with hematological malignancy at our centre.

Patients with NAC were more commonly exposed to antifungal agents prior to the episode of candidaemia, either in the form of prophylaxis or empirical therapy. However, our observational study is a subject to the bias of retrospective data collection, which might limit us from distinguishing between prophylactic or empirical antifungal therapy strategies. Apart from that, this study revealed that there was a great proportion of cases received delayed initiation of antifungal (> 48 hours after blood culture). Medical wards (general and high dependency wards) were both unexpectedly showed tendency towards deferment of antifungal initiation (day 3 onwards). This discovery is of a great concern as a delay in the initiation of antifungal therapy in hospitalized patients with candidaemia significantly impacted mortality.[13] Delaying antifungal therapy appears to be a common practice.

Notably, our proportion for Fluconazole-resistant isolates (27.6%) and Echinocandin-resistant isolates (10.2%) were high if compared to the previous studies.[14-16] All non-*albicans* strains were susceptible to Fluconazole except for *C.krusei* isolates. Yet, these data could be misleading and limited availability of susceptibility testing results should be taken into consideration. Fluconazole-resistant isolates have been reported to occur in immunosuppressed patients who are taking fluconazole chronically for prophylaxis.[17] This is consistent with our study findings that 57.9% and 57.2% of patients with prior antifungal therapy and breakthrough candidaemia exhibited reduced susceptibility towards Fluconazole, respectively.

Overall 30-day mortality in patients with candidemia was 59% %, which was not significantly different between *C. albicans* and NAC group. Although Moran *et al*.reported that an increased mortality rate and cost was noted in an adult population with NAC candidemia in the United States,[18] several other studies failed to identify a difference in the mortality rate between patients with C. albicans or NAC candidemia.[19,20] *C. albicans* is known to be more virulent than non-*albicans Candida spp*.[3] Candida infections are not solely related to the pathogenicity of the *Candida spp*, but also to complications associated with the patient's underlying illnesses. Furthermore, almost half of patients who died in association with candidaemia had at least two underlying illnesses. Certainly, the severity of a patient's underlying medical condition greatly influences mortality and its associated factors in different study populations. Our study did not assess the severity of underlying illness prior to the onset of candidaemia. Another factor need to be considered is timing for initiation of appropriate antifungal therapy. Delayed time to initiate appropriate antifungal therapy might explain the high number of mortality cases, although our study did not show statistical significance. Prompt antifungal therapy might influence the outcome as noted in the study by Chen *et al*.[15] However, the difference of time from onset of candidemia to effective antifungal therapy among fatal cases was not significant in our study.

More studies with larger sample size and adjusting all the factors influencing mortality are necessary to make a conclusion on the outcome of patients. Perhaps, a prospective nature of study with a larger sample size is needed in studying the impact of delayed antifungal initiation in candidaemia.

Furthermore, we included all-cause mortality at 30 days after diagnosis in our analyses, which might considerably influence the overall mortality in candidaemia at this center.

The major limitation of this study is its retrospective design with multiple comorbidites among patients and small sample sizes when attempting a subgroup analysis. However, our findings still offer valuable points in the management of patients with candidemia. Therefore, increased awareness of possible candidaemia is crucial and shall prompt an immediate diagnostic effort and antifungal treatment and reduce the risk of morbidity and mortality in candidaemia, particularly in medical settings.

Table 2 Antifungal susceptibility testing of *Candida spp* isolated from blood culture

Species	Susceptible	Intermediate	SDD	Resistant	MIC	
(total no of isolates)	n (%)	n(%)	n (%)	n (%)	Median (IQR)	Range
***C. albicans* (27)**						
Fluconazole[a]	18(66.7)	NA	NA	5(18.5)	3.5(5.56)	0.02-256
Amphotericin[a]	22(81.5)	NA	NA	1(3.7)	0.29(0.72)	0.002-1.5
Voriconazole[b]	16(59.3)	NA	2(8.7)	4(14.8)	0.13(0.70)	0.012-32
Caspofungin[c]	20(74.1)	NA	NA	2(7.4)	0.75(0.95)	0.064-32
***C. glabrata* (27)**						
Fluconazole[d]	1(3.7)	NA	7(25.9)	12(44.4)	160.0(224.0)	2-256
Amphotericin[d]	18(66.7)	1(3.7)	NA	1(3.7)	0.75(1.44)	0.02-32
Voriconazole[e]	14(51.9)	NA	2(7.4)	3(11.1)	1.5(0.94)	0.38-32
Caspofungin[e]	18(66.7)	NA	NA	1(3.7)	0.75(1.26)	0.002-2
***C. parapsilosis* (34)**						
Fluconazole[f]	17(50.0)	NA	4(11.8)	4(11.8)	3.00(22.0)	0.75-256
Amphotericin B[f]	23(67.6)	2(5.9)	NA	NA	0.50(0.91)	0.004-3
Voriconazole[g]	22(64.7)	NA	1(2.9)	NA	0.13(0.08)	0.032-2
Caspofungin[g]	20(58.8)	NA	NA	3(8.8)	1.5(0.76)	0.19-32
***C. tropicalis* (33)**						
Fluconazole[h]	18(54.5)	NA	2(6.1)	7(21.2)	2.00(99.0)	0.75-256
Amphotericin B[h]	24(72.7)	3(9.1)	NA	NA	0.25(1.41)	0.002-3
Voriconazole[i]	19(57.6)	NA	2(6.1)	5(15.2)	0.19(2.16)	0.047-32
Caspofungin[i]	24(72.7)	NA	NA	2(6.1)	0.75(1.25)	0.016-4
***C. krusei* (2)**						
Fluconazole	NA	NA	2(100.0)	NA	32(0)	32-32
AmphotericinB	1(50.0)	NA	NA	1(50.0)	4.37(5.12)	0.75-8
Voriconazole	2(100.0)	NA	NA	NA	0.5(0)	0.5-05
Caspofungin	2(100.0)	NA	NA	NA	1.06(1.33)[n]	0.125-2
***C. guillermondii* (5)**						
Fluconazole[j]	2(40.0)	NA	120.0)	1(20.0)	144.0(158.34)	32-256
Amphotericin B[j]	1(20.0)	1(20.0)	NA	2(40.0)	17.0(31.3)	0.25-32
Voriconazole[k]	NA	NA	NA	2(40.0)	32.0(0)	32
Caspofungin[k]	2(40.0)	NA	NA	NA	0.56(0.62)[n]	0.125-1
***C. rugosa* (2)**						
Fluconazole[l]	1(50.0)	NA	NA	NA	8(0)	8
Amphotericin B[l]	NA	1(50.0)	NA	NA	3(0)	3
Voriconazole[l]	1(50.0)	NA	NA	NA	0.19(0)	0.19
Caspofungin[l]	NA	NA	NA	-1(50.0)	3	3
***C. dubliniensis* (2)**						
Fluconazole	2(100.0)	NA	NA	NA	3(0)	0.75-3.0
Amphotericin B	2(100.0)	NA	NA	NA	0.02(0)	0.02-0.50
Voriconazole	2(100.0)	NA	NA	NA	0.032(0)	0.032-0.32
Caspofungin	1(50.0)	NA	NA	1(50.0)	2(1.41)	1-3

Unspecified *Candida* sp (2)						
Fluconazole[l]	NA	NA	1(50.0)	NA	32.38(44.72)[q]	0.75-64
Amphotericin B[l]	1(50.0)	NA	NA	NA	0.63(0.18) [q]	0.5-0.75
Voriconazole[l]	1(50.0)	NA	NA	NA	0.26(0.09) [q]	0.19-0.32
Caspofungin[l]	1(50.0)	NA	NA	NA	2.50(0.71) [q]	2-3
Total (134)						
Fluconazole[n]	59(56.2)	NA	17(16.2)	29(27.6)	6.0(62.0)	0.02-256
Amphotericin B[n]	92(87.6)	8(7.6)	NA	5(4.8)	0.38(0.93)	0.002-64
Voriconazole[o]	77(78.6)	NA	7(7.1)	14(14.3)	0.19(0.141)	0.012-32
Caspofungin[p]	88(89.8)	NA	NA	10(10.2)	1.00(1.12)	0.002-32

Antifungal susceptibility not available in;
[a] 4(14.8); [b] 7(25.9);[c] 5(18.5); [d] 7(25.9); [e] 8(29.6); [f] 9(26.5);
[g] 11(32.4); [h] 6(18.2); [i] 7(21.2);[j] 1(20.0); [k] 3(60.0); [l] 1(50.0);
[m] 1(33.3); [n]29(21.6)' [o]38(28.4);[p]36(26.9)
[q] Mean(SD)
NA Category not applicable

Table 3 Demographic profile and clinical characteristics of 79 patients who died with associated candidaemia

Characteristics	*Candida* species, n (%)		p value
	C.albicans **(n=17)**	**NAC (n=62)**	
Age (mean ± SD)	58.0 ±23.0	55.5±18.0	0.816
Sex			
Male	8(47.1)	37(59.7)	0.352
Female	9(52.9)	25(40.3)	
Race			
Malay	15(88.2)	56(90.3)	0.824
Chinese	2(11.8)	3(4.8)	
Siamese	-	1(1.6)	
Others	-	2(3.2)	
Underlying illness			
Diabetes mellitus	8(47.1)	32(51.6)	0.740
Dialysis dependent	3(42.9)	17(56.7)	0.512
Surgical condition	6(35.3)	35(56.5)	0.128
Hematological malignancy	3(17.6)	7(11.3)	0.489
Solid tumor	6(35.3)	6(9.7)	0.014
≥ 2 underlying illnesses	8(47.1)	29(46.8)	0.983
Predisposing factors			
Hemodynamic status			
Stable	5(29.4)	11(17.7)	0.294
In septic shock	12(76.5)	51(82.3)	
Septicaemia	9(52.9)	35(56.5)	0.796
Ongoing chemotherapy	1(5.9)	7(11.3)	0.801
Central venous catheterization	16(94.1)	60(96.8)	0.096
Urinary catheterization	17 (100.0)	60 (96.8)	0.999
Total parenteral nutrition	8(47.1)	25(40.3)	0.955
Mechanical ventilation			
Invasive	11(64.7)	42(67.7)	0.994
Non invasive	1(5.9)	1(1.6)	0.374
Duration of ventilation[a]	6(6)	11(17.7)	0.447
Prior antifungal therapy	3(17.6)	11(17.7)	0.993
≥ 2 factors	8(47.1)	29(46.8)	0.983
Time to initiate antifungal [b]			
Day 0 (culture day)	5(38.5)	14(31.8)	0.638
Day 1	2(15.4)	6(13.6)	0.943
Day 2	4(30.8)	9(20.5)	0.783
Day ≥ 3	2(15.4)	15(34.1)	0.282
Systemic antimicrobial therapy	14(82.4)	50(80.6)	0.874
Duration of antibiotic (days)[a]	14.0(19)	12.5(22)	0.754

Investigation profiles			
ANC count			
<1.00 (x 10^9/L)	3(67.6)	7(11.3)	0.489
≥1.00(x 10^9/L)	14(82.4)	55(88.7)	
Platelet count			
<20000/mm^3	1(5.9)	9(14.5)	0.447
2000 to 100000/mm^3	5(29.4)	21(37.1)	
>100000/mm^3	11(64.7)	30(48.4)	

[a]Median(IQR)
[b] 22 death cases did not receive treatment

Table 4 Significant factors in 79 mortality candidaemia cases (simple logistic regression)

Parameters	B	Crude OR	95%CI	p value
Surgical illness	-0.866	0.421	0.138,1.282	0.128
Solid tumor	1.627	5.09	1.38,18.74	0.014
Central venous catheterization	-2.096	0.123	0.01,1.448	0.096
WBC	0.024	1.024	0.994,1.055	0.116

ACKNOWLEDGEMENT

Bismillahirrahmanirrahim

My special thanks to my supervisor and co-supervisor, Dr Alwi Besari and Dr Azian Harun respectively, who had helped tremendously in the study with their ideas and expertise.

My gratitude also goes to Prof Syed Hateem Nor and Dr Siti Azrin for their help in statistics.

Many heartfelt thanks to all lecturers in the Department of Internal Medicine and all staff from School of Medical Sciences, USM.

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