

The clinical outcomes and predictive factors for in-hospital mortality in non-neutropenic patients with candidemia

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Abstract

Recent epidemiologic studies have showed that candidemia is an important nosocomial infection in hospitalized patients. The majority of candidemia patients were non-neutropenic rather than neutropenic status. The aim of this study was to determine the clinical outcome of non-neutropenic patients with candidemia and to measure the contributing factors for mortality. A total of 163 non-neutropenic patients with candidemia during January 2010 to December 2013 were retrospectively enrolled. The patients' risk factors for mortality, clinical outcomes, treatment regimens, and *Candida* species were analyzed. The overall mortality was 54.6%. *Candida albicans* was the most frequent *Candida* species (n=83; 50.9% of patients). Under multivariate analyses, hemodialysis (OR, 4.554; 95% CI, 1.464–14.164) and the use of amphotericin B deoxycholate (OR, 8.709; 95% CI, 1.587–47.805) were independent factors associated with mortality. In contrast, abdominal surgery (OR, 0.360; 95% CI, 0.158–0.816) was associated with a better outcome. The overall mortality is still high in non-neutropenic patients with candidemia. Hemodialysis and use of amphotericin B deoxycholate were independent factors associated with mortality, whereas prior abdominal surgery was associated with a better outcome.

Abbreviations: APACHE=Acute Physiology and Chronic Health Evaluation, CI=confidence intervals, ESCMID=European Society for Clinical Microbiology and Infectious Diseases, ICU=intensive care unit, IDSA=Infectious Disease Society of America, NPV=negative predictive value, OR=odds ratios, PPV=positive predictive value, SEM=standard error of the mean, SOFA=sequential organ failure assessment.

Keywords: candidemia, fungus, mortality, predictive factor

1. Introduction

Recent epidemiologic studies have showed that candidemia is an important nosocomial infection in hospitalized patients.^[1] Candidemia is reported to be the fourth most common blood stream infection in United States and seventh in Europe.^[2,3] The high prevalence of candidemia is caused by several factors such as invasive procedures, broad-spectrum antibiotics, and prolonged survival.^[4,5] In spite of the introduction of new antifungal medications during last 2 decades, the mortality rates of candidemia remained high, ranging from 37.9% to

61.8%.^[6–10] The risk factors attributed to mortality are old age, neutropenia, abdominal surgery, total parenteral nutrition, acute renal failure, hemofiltration procedures, corticosteroids treatment, malnutrition, diabetes mellitus, malignancy, and invasive mechanical ventilation.^[6–10]

Previous reports have showed that neutropenia is a significant risk factor for acquiring candida infection and the mortality in this subgroup is extremely high.^[11] However, the majority of candidemia patients were non-neutropenic rather than neutropenic status. The percentage of non-neutropenic patients ranged from 83 to 94% in patients with candidemia.^[10,12] In 2009, Infectious Disease Society of America (IDSA) published their guidelines.^[13] The recommendation for the first-line treatment of candidemia in non-neutropenic patients was fluconazole or echinocandin. The use of echinocandin was recommended in patients with moderate to severe illness or with recent azole exposure. However, the 2012 European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and 2016 IDSA guidelines both recommend administration of all echinocandins in non-neutropenic patients with candidemia.^[14,15] In addition, both guidelines recommend fluconazole to be the alternative therapy in this subgroup of patients. Considering the majority of patients with candidemia, the clinical outcomes of non-neutropenic patients deserve further elucidation. Although previous studies have investigated the outcomes of non-neutropenic patients with candidemia, most of the patients in these studies received amphotericin B or fluconazole therapy due to their study year.^[16,17] The effects of administration of amphotericin B, fluconazole therapy, and echinocandin on clinical outcomes deserve further investigation.

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The aim of this study was to determine the clinical outcome of non-neutropenic patients with candidemia. In addition, this study tried to measure the mortality-contributing factors including underlying comorbidity, intervention, and antifungal therapy.

2. Material and methods

2.1. Study population

The study retrospectively recruited patients with blood culture-confirmed *Candida species* from January 2010 to December 2013 in Chang Gung Memorial Hospital, a tertiary hospital in Taiwan. Patients under 18 years were excluded. The Chang Gung Medical Foundation Institutional Review Board approved the study (104-7578B) and waived the requirement for informed consent due to the retrospective nature of this study.

2.2. Study design

Each patient's medical records were reviewed to collect the clinical characteristics and laboratory results. In addition, the study analyzed the patients' information, which included Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, mechanical ventilation, diabetes mellitus, neoplasia, ablative chemotherapy, immunosuppressive agents, intensive care unit (ICU) admission, bone marrow transplant, solid organ transplant, neutropenia, corticosteroid therapy, trauma, prior surgery, intravascular catheter, urinary catheter, total parenteral nutrition, hemodialysis, antimicrobial therapy, and distribution of *Candida species*.

2.3. Definitions

Candidemia was defined as patients who had at least 1 *Candida*-positive blood culture. Corticosteroid therapy was defined as a dose equivalent at least 0.5 mg/kg per day of prednisolone administered for at least 7 days. Neutropenia was defined as absolute neutrophil count < 1000 cells/ μ L. Prior surgery was defined as patients who had undergone any surgery within 30 days preceding the onset of candidemia. In addition, hemodialysis was defined as patients received hemodialysis within 30 days preceding the onset of candidemia. Total parenteral nutrition was defined as patients receiving total parenteral nutrition for >7 days within 30-day period before the onset of candidemia.^[11] Ablative chemotherapy refers to the administration of alkylating agents, at doses that will not allow autologous hematologic recovery.^[18] Effective antifungal therapy was defined as the recommended dose for each antifungal was reached (at least 400 mg of fluconazole per day and 0.5 mg/kg per day of amphotericin B). Lower dose was accepted only in the case of renal impairment. Antifungal therapy administered within 24 hours of culture was also recorded.

2.4. Statistical analysis

Data were analyzed with SPSS (version 13.0; SPSS; Chicago, IL) statistical software. Continuous variables were expressed as mean \pm SEM (standard error of the mean). Student's *t* test was used for comparisons of normally distributed variables between 2 groups. Non-normally distributed data were compared by the Mann-Whitney test. Categorical variables were analyzed with chi-squared tests. All variables were primarily analyzed with univariate analysis. Those variables with a *P* value < 0.1 in the univariate analysis were then entered into the multivariate logistic

regression analysis model to determine their net effects on in-hospital mortality. Odds ratios (OR) and their 95% confidence intervals (CI) were used to assess the independent contribution of prognostic factors. A *P*-value of < 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of patients

A total of 169 candidemia patients were recruited during the study period. There were 6 patients with neutropenia, and 163 patients were non-neutropenic. The 163 non-neutropenic patients were enrolled for analysis. Among these non-neutropenic patients with candidemia, 89 (54.6%) died in the hospital. The baseline demographics and clinical characteristics of these patients are listed in Table 1. The mean ages of survivors and fatalities were 63.0 ± 18.3 and 69.2 ± 13.6 years, respectively. The incidence of effective antifungal therapy and antifungal therapy within 24 hours of culture were similar in both groups.

The source of candidemia included intravascular catheter (*n* = 66, 40.5%), intra-abdominal source (*n* = 32, 19.6%), the urinary tract (*n* = 11, 6.7%), other source (*n* = 8, 4.9%), and unknown source (*n* = 46, 28.2%).

3.2. Factors associated with mortality and predictive factors for mortality

Univariate analyses identified several factors associated with mortality, including the presence of ICU admission, mechanical ventilation, abdominal surgery, hemodialysis, intravascular catheter, corticosteroid therapy, and the use of amphotericin B deoxycholate (Table 1). There were 14 patients received amphotericin B therapy. All of them received amphotericin B deoxycholate. No patient received liposomal amphotericin B. Table 2 listed the results of multivariate analysis for the factors associated with mortality. Under multivariate analyses, hemodialysis (OR, 4.554; 95% CI, 1.464–14.164) and the use of amphotericin B deoxycholate (OR, 8.709; 95% CI, 1.587–47.805) were independent factors associated with mortality. In contrast, abdominal surgery (OR, 0.360; 95% CI, 0.158–0.816) seemed associated with a better outcome. The SOFA score in patients received amphotericin B deoxycholate was higher than those received other antifungal therapy (8.6 ± 0.7 vs 5.8 ± 0.5 , *P* = 0.023).

The sensitivities for predicting mortality in hemodialysis, use of amphotericin B deoxycholate, and abdominal surgery were 84.9%, 85.7%, and 45.2%, respectively (Table 3). Both hemodialysis and the use of amphotericin B deoxycholate had a good negative predictive value (93.2% and 97.3% respectively). Therefore, the absence of those features may predict the absence of mortality.

3.3. Distribution of *Candida species*

Candida albicans was the most frequent *Candida species* (*n* = 83; 50.9% of patients), followed by *C tropicalis* (*n* = 32; 19.6% of patients), *C parapsilosis* (*n* = 28; 17.2% of patients), and *C glabrata* (*n* = 15; 9.2% of patients) (Table 4). Furthermore, the presence of *C tropicalis* in fatalities group was 25.8%, which was significantly higher than that in the survivor group (12.2%, *P* = 0.029). In contrast, the presence of *C parapsilosis* in the fatalities group was significantly lower than the survivor group (11.2% vs 24.3%, *P* = 0.027). The SOFA score in the *C tropicalis* subgroup was higher than other species (7.9 ± 0.7 vs 5.9 ± 0.5 , *P* = 0.045).

Table 1**Demographic characteristics and risk factors.**

	Total n = 163	Fatalities n = 89	Survivors n = 74	P value	OR	95% CI
Demographic characteristics						
Age, year	66.4 ± 16.1	69.2 ± 13.6	63.0 ± 18.3	0.017	1.025	1.005–1.046
Male, n (%)	90 (55.2)	53 (59.6)	37 (50)	0.222	1.657	0.756–3.633
ICU admission, n (%)	65 (39.9)	45 (50.6)	20 (27)	0.002	2.761	1.427–5.344
SOFA score	5.6 ± 0.5	6.1 ± 0.6	4.3 ± 0.9	0.127	0.865	0.716–1.044
APACHE II score	16.5 ± 1.3	17.4 ± 1.7	14.5 ± 1.7	0.294	0.962	0.894–1.035
Underlying condition or risk factor						
Variables	Total	Fatalities	Survivors	P value	OR	95% C.I.
Diabetes mellitus, n (%)	57 (35.0)	36 (40.4)	21 (28.4)	0.108	2.067	0.843–5.072
Trauma, n (%)	9 (5.5)	3 (3.4)	6 (8.1)	0.302	1.041	0.166–6.533
Mechanical ventilation, n (%)	87 (53.4)	62 (69.7)	25 (33.8)	<0.001	3.633	1.478–8.926
Neoplasia, n (%)	71 (43.6)	43 (48.3)	28 (37.8)	0.179	2.490	1.050–5.904
Urinary catheter, n (%)	114 (69.9)	67 (75.3)	47 (63.5)	0.103	1.272	0.602–2.685
Abdominal surgery, n (%)	48 (29.4)	20 (22.5)	28 (37.8)	0.032	0.476	0.240–0.944
Nonabdominal surgery, n (%)	28 (17.2)	15 (16.9)	13 (17.6)	0.902	0.951	0.420–2.152
Hemodialysis, n (%)	33 (20.2)	28 (31.5)	5 (6.8)	<0.001	6.334	2.303–17.467
Solid organ transplant, n (%)	1 (6.1)	1 (1.1)	0	1.000	1.011	0.898–1.034
Intervention						
Any intravascular catheter, n (%)	132 (81.0)	79 (88.8)	53 (71.6)	0.005	2.772	0.865–8.882
Antimicrobial therapy, n (%)	163 (100)	89 (100)	74 (100)	–	–	–
Total parenteral nutrition, n (%)	53 (32.5)	31 (34.8)	22 (29.7)	0.489	1.005	0.372–2.716
Corticosteroid therapy, n (%)	59 (36.2)	42 (47.2)	17 (23.0)	0.001	2.996	1.513–5.933
Ablative chemotherapy, n (%)	9 (5.5)	7 (7.9)	2 (2.7)	0.184	1.923	0.281–13.167
Other immunosuppressive agents, n (%)	1 (6.1)	1 (1.1)	0 (0)	1.000	1.011	0.898–1.034
Antifungal therapy						
Amphotericin B deoxycholate, n (%)	14 (8.6)	12 (13.5)	2 (2.7)	0.022	5.610	1.214–25.937
Fluconazole, n (%)	122 (74.8)	66 (74.2)	56 (75.7)	0.824	0.922	0.452–1.880
Voriconazole, n (%)	3 (1.8)	2 (2.2)	1 (1.4)	0.672	1.678	0.149–18.88
Caspofungin, n (%)	6 (3.7)	5 (5.6)	1 (1.4)	0.150	4.345	0.496–38.07
Micafungin, n (%)	8 (4.9)	4 (4.5)	4 (5.4)	0.789	0.824	0.199–5.816
Anidulafungin, n (%)	20 (12.3)	14 (15.7)	6 (8.1)	0.140	2.116	0.770–5.816
Effective antifungal therapy, n (%)	143 (87.7)	81 (91.0)	62 (83.8)	0.161	1.960	0.755–5.088
Antifungal therapy within 24 hours of culture, n (%)	89 (54.6)	53 (59.6%)	36 (48.6)	0.164	1.554	0.834–2.895

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; SOFA score, Sequential Organ Failure Assessment score.

In contrast, patients with *C parapsilosis* infection had a lower SOFA score than those infected with other species (1.3 ± 0.9 vs 6.6 ± 0.4 , $P = 0.013$).

4. Discussion

The present study demonstrated that mortality of patients with candidemia was as high as 54.6%. Among the pathogens, *C albicans* (50.9%) was still the most common species in candidemia, followed by *C tropicalis* (19.6%). Hemodialysis

and use of amphotericin B deoxycholate were independent factors for mortality. In contrast, prior abdominal surgery was associated with a better outcome.

Previous studies have demonstrated that candidemia patients who had undergone prior abdominal surgery had a lower mortality rate than those without. In addition, prior abdominal surgery is an independent predictor for survival in candidemia patients.^[11] Compatible with previous evidence, our study also demonstrated that prior abdominal surgery was independently associated with survival in candidemia patients. One possible reason for association between prior abdominal surgery and a better outcome may be the rapid control of infection route by means of appropriate surgical intervention. Several reports have specifically identified the benefit of surgical procedures when deep-seated candida infection developed in the intestine.^[19,20] In addition, the majority of medical patients with candidemia had underlying comorbidities. In patients with underlying comorbidities, candidemia may reflect the impairment of the immune response. Increased mortality in medical patients with candidemia may be contributed by the failure of the host immune system to control its own gut flora including *Candida* species.

Emergent evidence has showed that hemodialysis is a risk factor for development of candidemia.^[21,22] In addition, hemodialysis is found to be independently associated with mortality in patients with candidemia.^[23–28] The contribution of

Table 2**Multivariate analysis of major factors associated with mortality in patients with candidemia.**

Variables	Odds ratio	95% CI	P value
Hemodialysis	4.554	1.464–14.164	0.009
Abdominal surgery	0.360	0.158–0.816	0.014
Use of amphotericin B deoxycholate	8.709	1.587–47.805	0.013
Mechanical ventilation	2.043	0.781–5.349	0.146
Age	0.982	0.957–1.006	0.146
Intravenous catheter	1.492	0.543–4.099	0.437
Use of corticosteroids	1.576	0.706–3.516	0.267
ICU admission	1.235	0.462–3.296	0.674

ICU, intensive care unit.

Table 3**Performances of Independent variables for prediction of mortality in patients with candidemia.**

Variables	Fatalities n, (%)	Survivors n, (%)	Sensitivity	Specificity	PPV	NPV	Likelihood ratio	
Hemodialysis	+	28/33	5/33	84.9 (68.1–94.9)	53.1 (44.1–61.9)	93.2 (84.9–97.8)	93.2 (84.9–97.8)	1.81
	–	61/130	69/130					
Use of Amphotericin B deoxycholate	+	12/14	2/14	85.7 (57.2–98.2)	48.3 (40.1–56.6)	97.3 (90.6–99.7)	97.3 (90.6–99.7)	1.66
	–	77/149	72/149					
Abdominal surgery	+	33/73	40/73	45.2 (35.5–57.3)	37.8 (27.8–48.)	46.0 (34.3–57.9)	46.0 (34.3–57.9)	0.73
	–	56/90	34/90					

NPV, negative predictive value; PPV, positive predictive value. Sensitivity, specificity, and predictive values are expressed as % (95% confidence interval).

Table 4**Candida bloodstream isolates recovered from patients.**

Candida Species	Total	Fatalities	Survivors	P value
<i>C albicans</i> , n (%)	83 (50.9)	51 (57.3)	32 (43.2)	0.074
<i>C glabrata</i> , n (%)	15 (9.2)	9 (10.1)	6 (8.1)	0.659
<i>C parapsilosis</i> , n (%)	28 (17.2)	10 (11.2)	18 (24.3)	0.027
<i>C tropicalis</i> , n (%)	32 (19.6)	23 (25.8)	9 (12.2)	0.029
<i>C guilliermondii</i> , n (%)	4 (2.5)	0	4 (5.4)	0.041
<i>C lusitanae</i> , n (%)	1 (0.6)	0	1 (1.4)	0.454
<i>C rugosa</i> , n (%)	1 (0.6)	0	1 (1.4)	0.454
<i>C famata</i> , n (%)	4 (2.5)	0	4 (5.4)	0.041
<i>C pelliculosa</i> , n (%)	1 (0.6)	1 (1.1)	0	1
Unknown/unidentified, n (%)	5 (3.1)	3 (3.4)	2 (2.7)	1
Polyfungal*, n (%)	7 (4.3)	5 (5.6)	2 (2.7)	0.457

* More than one candida species was isolated from a blood culture.

hemodialysis to mortality may be partially explained by the high incidence of hemodialysis catheter or routes.^[25,26,28] In our study, both intravenous catheter and hemodialysis were significant predictors for mortality in univariate analysis. However, only hemodialysis remains significant in predicting mortality after multivariate analysis. Thereafter, the association between hemodialysis and mortality may be better explained by the impaired immune response in patients who have received hemodialysis.

Amphotericin B deoxycholate has previously been widely used in therapy of systemic fungal infection. Amphotericin B deoxycholate has many adverse effects including fever, chills, gastrointestinal upset, electrolyte imbalance, and most importantly acute renal failure.^[29] In patients received amphotericin B therapy for systemic fungal infection, when renal failure developed, the mortality rate was much higher than those without renal failure.^[30] Our study also demonstrated that use of amphotericin B deoxycholate was associated with increased mortality in candidemia patients. The illness severity, indicated by the SOFA score, in patients received amphotericin B deoxycholate was higher than those received other antifungal therapy. Therefore, the association between use of amphotericin B deoxycholate and mortality may be attributed by the higher illness severity in patients received amphotericin B therapy than those received other antifungal therapy. Therefore, amphotericin B should be used with caution for patients with candidemia.

Compatible with previous study,^[31] our results demonstrated that *C tropicalis* infection was associated with increased risk of mortality. Conversely, *C parapsilosis* infection was associated with lower mortality than other species. In our study, the SOFA score in the *C tropicalis* subgroup was higher than other species.

Patients with *C parapsilosis* infection had lower SOFA score than those infected with other species. Therefore, the illness severity may play an important role in the difference of mortality risk among candida species. In addition, previous studies had showed that the occurrence of *C parapsilosis* fungemia related to long-term use of central venous catheter.^[32] The central venous catheter is an easily removable source of infection. The easy removal of infection source may also contribute to the decreased mortality.

The present study is limited by its retrospective nature and relatively small sample size. Therefore, some bias in patient selection or statistic analysis may be existed in the study. To further confirm the results of the study, a prospective study with larger sample size is needed to evaluate the clinical outcomes in non-neutropenic patients with candidemia.

In conclusion, the mortality rate is still high in non-neutropenic patients with candidemia. The prevalence of non-albicans *Candida* species was up to 49.1%. Hemodialysis and use of amphotericin B deoxycholate were independent factors associated with mortality, whereas abdominal surgery was associated with a better outcome. In addition, the hemodialysis and the use of amphotericin B deoxycholate were effective at negatively predicting mortality rates.

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