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Retrospective analysis of mortality and *Candida* isolates of 75 patients with candidemia: a single hospital experience

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Ryuichi Hirano[1]
Yuichi Sakamoto[2]
Kumiko Kudo[1]
Motoki Ohnishi[3]

[1]Department of Pharmacy, Aomori Prefectural Central Hospital, Aomori, Japan; [2]Laboratory Medicine and Blood transfusion, Aomori Prefectural Central Hospital, Aomori, Japan; [3]General Medicine, Aomori Prefectural Central Hospital, Aomori, Japan

Abstract: The mortality rate for candidemia is approximately 30%–60%. However, prognostic factors in patients with candidemia have not yet been elucidated in detail. The aim of the present study was to analyze prognostic factors for candidemia using the mortality rate and *Candida* isolates of patients with candidemia. Seventy-five patients with candidemia were analyzed between January 2007 and December 2013. The main outcome of this study was the 30-day mortality rate after the diagnosis of candidemia. The acute physiology and chronic health evaluation II score (APACHE II score) was measured in 34 patients (45.3%). Odds ratios (ORs) for death due to candidemia were analyzed using a multivariate stepwise logistic regression analysis. Twenty (26.6%) patients died within 30 days of being diagnosed with candidemia. Non-survivors had a significantly higher APACHE II score (n=7, mean; 18.9±4.5) than that of survivors (n=27, mean; 14.0±5.0). Advanced age (OR =1.1, 95% confidence interval =1.01–1.23, *P*=0.04) was a significant risk factor for a high mortality rate, whereas removal of a central venous catheter (OR =0.03, 95% confidence interval =0.002–0.3, *P*=0.01) was associated with a lower mortality rate. Seventy-six *Candida* spp. were isolated from blood cultures: *Candida albicans* 28 (36.8%), *Candida parapsilosis* 23 (30.2%), *Candida guilliermondii* 16 (21.0%), *Candida glabrata* four (5.2%), *Candida tropicalis* two (2.6%), and *Candida* spp. three (3.9%) that could not be identified. *C. parapsilosis* was the most frequently isolated species in younger patients (<65 years), whereas *C. albicans* was the most frequently isolated in elderly patients (≥65 years). Physicians who treat candidemia need to consider removing the central venous catheter and pay attention to the general condition of patients, particularly that of elderly patients.

Keywords: aging, *Candida*, candidemia, central venous catheter, Japan

Introduction

Candida spp. are ranked as the fourth main cause of bloodstream infections in hospitals, and the frequency of candidemia has increased in recent years.[1] The mortality rate for candidemia is approximately 30%–60%, and the prognosis is generally poor.[2] Invasive medical technologies, such as the use of immunosuppressive agents or anticancer drugs via central venous catheters (CVCs), are associated with the development of candidemia.[3] Therefore, an early diagnosis and treatment are more important for improving the outcome of patients with candidemia due to the increased use of invasive medical technologies in recent years.[4]

Fifteen *Candida* spp. have been isolated from inpatients[3] and the susceptibilities of these species to various antifungal agents differ, with *Candida albicans* being sensitive to many antifungal agents. Among the non-albicans *Candida* spp., *Candida parapsilosis* is resistant to micafungin, and *Candida glabrata* exhibits low sensitivity to many azole antifungals. The proportions of *Candida* isolates also vary among regions. *C. glabrata*

Correspondence: Ryuichi Hirano
Department of Pharmacy, Aomori Prefectural Central Hospital,
2-1-1 Higashi-tsukurimichi, Aomori-shi, Aomori 030 8553, Japan
Tel +81 17 726 8007
Fax +81 17 726 8325
Email r.hirano1115@gmail.com

is generally more common in Western countries, whereas *Candida tropicalis* is more common in Asia.[3] A surveillance study conducted between 2001 and 2002, a time during which echinocandin antifungal agents were not used in Japan, isolated *C. albicans*, *C. parapsilosis*, and *C. glabrata* from 40%, 23%, and 18% of candidemia cases, respectively.[5] Forrest et al reported correlations between the increased use of echinocandin antifungal agents and higher incidence of *C. parapsilosis* candidemia, as well as with reductions in *C. tropicalis* and *C. glabrata* candidemia.[6] However, difficulties are associated with basing strategies on the findings of previous surveillance studies because some reported that the emergence of echinocandin antifungal agents changed the proportions of different *Candida* spp. isolates in candidemia.[6,7] If a yeast-like fungus is isolated from a blood culture, early empirical treatment must be initiated to improve the outcome of the patient;[4] however, the antifungal agents recommended for the treatment of candidemia vary according to the species isolated. Since few studies have been conducted on the prognostic factors of candidemia mortality in Japan, they remain unclear in patients with candidemia. Thus, the treatment of candidemia needs to be optimized to investigate the risk factors for death and determine the proportions of different isolates in each hospital.

In the present study, we performed a retrospective analysis of the candidemia cases that occurred in our hospital in order to identify the prognostic factors of and proportions of different isolates in candidemia.

Materials and methods

Study design and population

Seventy-five patients diagnosed with candidemia in Aomori Prefectural Central Hospital between January 2007 and December 2013 were enrolled in this study. This is a general hospital with 695 beds and is located in Aomori City, Japan. Based on medical records, we included patients with symptoms of infection (eg, fever up to 37°C) and with at least one positive blood culture for *Candida* spp. Patients without symptoms of infection were excluded from this study. The main outcome of the present study was the 30-day mortality rate after the diagnosis of candidemia, as described previously.[8–10] The study protocol was approved by the Ethics Committee of Aomori Prefectural Central Hospital. Investigations were carried out by securing each patient's anonymity.

Definitions of each disease and clinical data collection

We assessed age, sex, complications, main disease, and antibiotics used. We confirmed in patients with CVC whether catheters were removed after the diagnosis of candidemia. We calculated the acute physiology and chronic health evaluation II score (APACHE II score) of 34 (45.3%) patients.[11] *Candida* endophthalmitis was diagnosed by an ophthalmologist based on the finding of fungal endophthalmitis.

We defined each disease state as follows. Patients who received cyclosporine, tacrolimus, anticancer drugs, or corticosteroids were defined as immunosuppression. Patients who had a neutrophil count <500 cell/μL at the time of the blood culture were defined as neutropenia. Patients who required dialysis or those with serum creatinine values ≥ 3.0 mg/dL were defined as renal failure. Patients who had more than five times the upper limit for aspartate transaminase, alanine transaminase, or gamma glutamyl transpeptidase were defined as liver failure. Patients who had underlying diseases such as asthma, pneumonia, lung abscess, and lung cancer were defined as lung disease. Patients who were 65 years of age or older were defined as elderly patients, whereas patients who were 64 years of age or younger were defined as younger patients. The cut-off value of age was determined by the median age of all patients.

Mycological data collection

Mycological data were collected from the records of each patient's blood culture tests. Blood culture tests were performed using a series of aerobic and anaerobic blood culture bottles with Bac T/ALERT, which were incubated in a Bac T/ALERT 3D blood culture system (SYSMEX; bioMerieux, Lyon, France). After Gram staining, blood cultures that tested positive for yeasts were subcultured on CHROM agar *Candida* culture medium (Kanto Chemical, Tokyo, Japan) and incubated for 48 hours at 30°C. *Candida* spp. were identified using the ID 32C system (SYSMEX; bioMerieux), and antifungal susceptibility tests were performed using the yeast-like fungal drug sensitivity kit ASTY (Kyokuto Pharmaceutical industrial, Tokyo, Japan). Resistance to fluconazole and micafungin were determined based on the minimum inhibitory concentration (MIC) after incubating for 48 hours at 35°C. We used species-specific antifungal drug susceptibility break points for fluconazole and micafungin according to the Clinical and Laboratory Standards Institute (CLSI) M27-S4.[12] Since there is currently no break point for fluconazole in *Candida guilliermondii*, epidemiological cut-off values (ECVs) were applied to determine susceptibility.[13] We defined three *Candida* spp. that could not be identified as others. ECVs for *C. guilliermondii* were also applied to others to determine susceptibility.[14] The ECVs for *C. guilliermondii* were as follows; resistant strains were defined as MIC ≥ 16 μg/mL for fluconazole and MIC ≥ 4 μg/mL for micafungin.[14]

Statistical analysis

Results were expressed as mean values ± standard deviation. Continuous data were analyzed using the Mann–Whitney *U* test, and categorical data were analyzed using the χ^2 test. $P<0.05$ was considered significant. We divided patients into survivors and non-survivors based on death within 30 days of being diagnosed with candidemia, and we evaluated the factors associated with death by comparing the treatment and clinical factors. Significant variants in the univariate analysis were selected for inclusion in a multivariate stepwise logistic regression analysis. We included age, the removal of CVC, lung disease, and infection with *C. albicans* and *C. parapsilosis* in a multivariate stepwise logistic regression analysis in order to determine the odds ratios (ORs) for death within 30 days of being diagnosed with candidemia. The factors associated with death among elderly patients by comparing the treatment and clinical factors between younger and elderly patients were also evaluated. We included immunosuppression therapy in a multivariate stepwise logistic regression analysis to determine the ORs for death among elderly patients with candidemia. We did not include the APACHE II score in a multivariate stepwise logistic regression analysis because it could not be calculated in more than half of all patients. All statistical analyses were performed using the Excel- Toukei 2012 (Social Survey Research Information Co, Ltd, Tokyo, Japan).

Results

Patient characteristics

Seventy-five patients were included in this study (51 males and 24 females, mean age; 62.1±19.4, age range; 5–94, age median; 65). Patient demographics, underlying diseases, diagnoses, and treatments for candidemia are shown in Table 1. Twenty (26.6%) patients died within 30 days of being diagnosed with candidemia. We calculated the APACHE II score of 34 (45.3%) patients (mean; 15.0±5.2, range; 6–27, median; 16.5). A total of 92% of patients had undergone central venous catheterization, 77.3% of patients required total parenteral nutrition therapy, and 90.6% of patients had low serum albumin levels.

Table 1 Characteristics of patients with candidemia

Characteristics	N	%
Number of cases	75	
Age (range)	62.1 (5–94)	
Sex (male)	51	68
Death within 30 days of candidemia diagnosis	20	26.6
Presence of CVC	69	92
Immunosuppressive therapy	30	40
Intensive care unit admission	7	9.3
Total parenteral nutrition	58	77.3
Mechanical ventilation	7	9.3
Renal failure	6	8
Liver failure	20	26.6
Low serum albumin (<2.5 mg/dL)	68	90.6
Organ transplantation	7	9.3
History of *Candida* colonization	7	9.3
Surgery	20	26.6
Neutropenia	6	8
Malignancy	41	54.6
Lung disease	14	18.6
Diabetes mellitus	16	21.3
Diagnosis of and treatment for candidemia		
Two sets of blood cultures	54	72
Examination of serum β-D glucan	53	70.6
Diagnosis of endophthalmitis due to *Candida* spp.	33	44
Removal of CVC	49	65.3
Antifungal agents		
Fosfluconazole	28	37.3
Micafungin	34	45.3
Voriconazole	2	2.6
Liposomal amphotericin B	7	9.3
Itraconazole	2	2.6

Abbreviation: CVC, central venous catheter.

Diagnosis and treatment of candidemia

In order to diagnose candidemia, two sets of blood cultures were obtained from 72% of patients. The serum β-D glucan level was examined in 70.6% of cases. A diagnosis of endophthalmitis due to *Candida* spp. was obtained in 44% of patients. Among the patients who received an ophthalmological consultation, two were diagnosed with *Candida* endophthalmitis caused by *C. albicans*. The CVC removal rate was 65.3%. Among the 73 patients who received antifungal agents, the treatments employed micafungin, fosfluconazole, liposomal amphotericin B, voriconazole, and itraconazole in 34 (45.3%), 28 (37.3%), seven (9.3%), two (2.6%), and two (2.6%) cases, respectively.

Mycological data of *Candida* spp.

Among the 76 *Candida* isolates from blood cultures, *C. albicans* accounted for 28 (36.8%), *C. parapsilosis* 23 (30.2%), *C. guilliermondii* 16 (21%), *C. glabrata* four (5.2%), *C. tropicalis* two (2.6%), and others three (3.9%). The number of total *Candida* isolates was 76 because one patient was diagnosed with a mixed infection of *C. parapsilosis* and *C. guilliermondii*. Of the 76 *Candida* isolates, eight strains (10.5%) exhibited resistance to fluconazole, ie, *C. parapsilosis*, two (8.6%); *C. guilliermondii*, two (12.5%); *C. tropicalis*, two (100%); and others, two (66.6%). Five strains (6.6%) were resistant to micafungin, ie, *C. albicans* (3.5%); *C. parapsilosis* (4.3%); *C. guilliermondii* (6.2%); *C. glabrata* (25%); and others (33.3%).

Factors associated with death

Patients were divided into survivors and non-survivors according to their 30-day mortality rates (Table 2). Non-survivors were older and had a higher rate of infection with *C. albicans* and lung disease than survivors. Non-survivors had a lower rate of CVC removal and lower rate of infection with *C. parapsilosis* than survivors. Non-survivors had a significantly higher APACHE II score (n=7, mean; 18.9±4.5) than that of survivors (n=27, mean; 14.0±5.0) according to the Mann–Whitney *U* test (*P*=0.02). The multivariate analysis identified two factors that had significant relationships with death due to candidemia: advanced age (OR =1.1, 95% confidence interval [CI] =1.01–1.23, *P*=0.04) was associated with a higher mortality rate than the removal of CVC (OR =0.03, 95% CI =0.002–0.3, *P*=0.01) (Table 3). We divided patients into two groups to investigate the risk factors for death among elderly patients with candidemia because the multivariate logistic regression analysis identified advanced age as a significant risk factor for death. We compared parameters between younger and elderly patients (Table 4). The mortality rate of candidemia was higher in elderly patients (33.3%, 14/42) than in younger patients (18.1%, 6/33); however, the χ^2 analysis showed that this difference was not significant (*P*=0.14). The rates of immunosuppression therapy and organ transplantation were lower in elderly patients than in younger patients. The Mann–Whitney *U* test revealed that elderly patients had a significantly higher APACHE II score (n=21, mean; 16.4±4.9) than that of younger patients (n=13, mean; 12.7±5.0) (*P*=0.04). No significant factors for death among elderly patients were identified in the multivariate analysis: immunosuppression therapy (OR =2.5, 95% CI =0.59–10.9, *P*=0.2).

Table 2 Comparison of various parameters among survivors and non-survivors

	Survivors (%)	Non-survivors (%)	*P*-value
Clinical demographics			
Number of cases	55	20	
Age*	59.1±20.6	70.5±11.5	0.03
Sex (male)	39	12	0.37
Presence of CVC	52 (94.5)	17 (85)	0.33
Immunosuppressive therapy	21 (38.1)	9 (45)	0.59
Intensive care unit admission	5 (9.1)	2 (10)	0.9
Total parenteral nutrition	43 (78.1)	15 (75)	0.76
Mechanical ventilation	4 (7.3)	3 (15)	0.37
Renal failure	4 (7.3)	2 (10)	0.7
Liver failure	12 (21.8)	8 (40)	0.11
Low albumin (<2.5 mg/dL)	49 (89.0)	19 (95)	0.43
Organ transplantation	4 (7.3)	3 (15)	0.3
History of *Candida* colonization	4 (7.3)	3 (15)	0.37
Surgery	16 (29.1)	4 (20)	0.56
Neutropenia	3 (5.5)	3 (15)	0.18
Malignancy	32 (58.1)	9 (45)	0.31
Lung disease*	7 (12.7)	7 (35)	0.028
Diabetes mellitus	11 (20)	5 (25)	0.64
Treatment for candidemia			
Removal of CVC*	44 (80)	5 (25)	<0.01
Fosfluconazole	21 (38.1)	7 (35)	0.8
Micafungin	27 (49.0)	7 (35)	0.27
Liposomal amphotericin B	5 (9.0)	2 (10)	0.9
***Candida* spp.**			
*Candida albicans**	16 (29.0)	12 (60)	0.023
*Candida parapsilosis**	22 (40)	1 (5)	<0.01
Candida guilliermondii	13 (23.6)	3 (15)	0.51
Resistance to fluconazole	4 (7.2)	4 (20)	0.11
Resistance to micafungin	4 (7.2)	1 (5)	0.72

Notes: Data are expressed as the mean ± standard deviation (SD; min–max). Statistical analyses were performed using the χ^2 test or Mann–Whitney *U* test. *Significant difference (*P*<0.05).
Abbreviation: CVC, central venous catheter.

Table 3 Risk factors for death within 30 days of being diagnosed with candidemia according to a stepwise regression analysis

Risk factors	Odds ratio	95% CI	*P*-value
Age	1.11	1.01–1.23	0.04
Removal of CVC	0.03	0.002–0.3	0.01
Lung disease	3.99	0.6–26.4	0.15
Candida albicans	6.2	0.4–96.7	0.19
Candida parapsilosis	0.12	0.005–2.9	0.19

Notes: A multivariate analysis was performed using a stepwise logistic regression model. Each factor was selected by a univariate analysis between survivors and non-survivors (*P*<0.05).
Abbreviations: CVC, central venous catheter; CI, confidence interval.

The 30-day mortality rates for each *Candida* spp. were as follows: *C. albicans*, 42.9% (12/28); *C. parapsilosis*, 4.3% (1/23); *C. guilliermondii*, 18.7% (3/16); *C. glabrata*, 25% (1/4); *C. tropicalis*, 100% (2/2); others, 33.3% (1/3). The χ^2 analysis revealed a significant difference in mortality rates between patients with *C. albicans* and *C. parapsilosis* (*P*<0.01).

Discussion

Since candidemia is a nosocomial infection with a high mortality rate,[8–10] it is important to optimize its treatment based on an accurate diagnosis and by determining the proportions of different isolates in each hospital. In the present study, the 30-day mortality rate of patients with candidemia was approximately 26%, which was consistent with previous findings.[8,9]

Approximately 20% of patients with candidemia develop *Candida* endophthalmitis.[15] In the present study, approximately 6% patients were diagnosed with *Candida* endophthalmitis, which is lower than that of previous findings. *C. albicans* has been identified as the species that

Table 4 Comparison of various parameters among younger and elderly patients with candidemia

	Younger patients (%)	Elderly patients (%)	*P*-value
Clinical demographics			
Number of cases	33	42	
Age*	44.1±14.4	76.3±7.2	<0.01
Sex (male)	22	29	0.82
Death within 30 days of candidemia diagnosis	6 (18.1)	14 (33.3)	0.14
Presence of CVC	31 (93.9)	38 (90.4)	0.58
Immunosuppressive therapy*	20 (60.6)	10 (23.8)	<0.01
Intensive care unit admission	2 (6.0)	5 (11.9)	0.45
Total parenteral nutrition	25 (75.7)	33 (78.5)	0.72
Mechanical ventilation	2 (6.0)	5 (11.9)	0.45
Renal failure	2 (6.0)	4 (9.5)	0.68
Liver failure	11 (33.3)	9 (21.4)	0.24
Low albumin (<2.5 mg/dL)	28 (84.8)	40 (95.2)	0.12
Organ transplantation*	7 (21.2)	0 (0)	<0.01
History of *Candida* colonization	5 (15.1)	2 (4.7)	0.12
Surgery	8 (24.2)	12 (28.5)	0.67
Neutropenia	5 (15.1)	1 (2.3)	0.08
Malignancy	18 (54.5)	23 (54.7)	0.98
Lung disease	5 (15.1)	9 (21.4)	0.48
Diabetes mellitus	6 (18.1)	10 (23.8)	0.58
Treatment for candidemia			
Removal of CVC	23 (69.6)	26 (61.9)	0.48
Fosfluconazole	11 (33.3)	17 (40.4)	0.52
Micafungin	15 (45.4)	19 (45.2)	0.98
Liposomal amphotericin B	3 (9.0)	4 (9.5)	1
***Candida* species**			
Candida albicans	10 (30.3)	18 (42.8)	0.26
Candida parapsilosis	12 (36.3)	11 (26.1)	0.34
Candida guilliermondii	6 (18.1)	10 (23.8)	0.55
Resistance to fluconazole	5 (15.1)	3 (7.1)	0.29
Resistance to micafungin	3 (9.1)	2 (4.7)	0.64

Notes: Data are expressed as the mean ± standard deviation (SD; min–max). Statistical analyses were performed using the χ^2 test or Mann–Whitney *U* test. *Significant difference ($P<0.05$).
Abbreviation: CVC, central venous catheter.

most frequently causes *Candida* endophthalmitis.[15] If the diagnosis and treatment of endophthalmitis are delayed, the patient may become blind. According to the treatment guidelines of the Infectious Diseases Society of America, an ophthalmological consultation to diagnose endophthalmitis is strongly recommended for all patients with candidemia.[16] The low rate of ophthalmological consultations was identified as a problem during the diagnosis of candidemia in our hospital.

Of the *Candida* spp. isolated from blood cultures in the present study, the frequency of *C. parapsilosis* was higher while that of *C. glabrata* was lower than previous findings reported in Japan.[5] *C. glabrata* is generally sensitive to micafungin, whereas *C. parapsilosis* has a high MIC.[5] Forrest et al reported that after the introduction of echinocandin antifungal agents, the frequency of *C. parapsilosis* isolates increased, whereas that of *C. glabrata* decreased.[6] In our hospital, micafungin has been used since 2004, and this drug is administered as a therapeutic as well as preventive agent to patients with suspected fungal infections. Therefore, the widespread use of micafungin is considered to be responsible for the specific proportions of isolates detected in our hospital, which differ from previous findings.[5] In the susceptibility tests using fluconazole and micafungin, eight strains were resistant to fluconazole (10.5%), and five strains were resistant to micafungin (6.5%), which is consistent with previous findings.[17]

We identified two factors that correlated with death due to candidemia: advanced age and a failure to remove CVC. Many cases of candidemia are attributable to CVC, and the prognosis of patients is improved by removing the focus of infection.[8,18] Our results indicated that persistent CVC was detrimental to patients with candidemia.

Previous studies identified advanced age as a significant risk factor for death among patients with candidemia.[8–10] However, few studies have investigated risk factors for death among elderly patients. We could not identify any significant risk factors for death among elderly patients with candidemia. Elderly patients with candidemia had markedly high APACHE II scores and were treated with mechanical ventilation, which were considered significant risk factors for death.[19] In our study, non-survivors had significantly higher APACHE II scores than those of survivors, and a significant difference was observed in this score between elderly and younger patients. The APACHE II score is a severity of illness index that is affected by the general condition of patients. Considering these results, poor general condition was considered to be responsible for the high mortality rate observed among elderly patients with candidemia.

Previous studies suggested that the proportion of non-albicans *Candida* spp. increases with age; *C. glabrata* was detected in 20% of patients aged ≥65 years.[20] Thus, our results differed from previous findings. Immunosuppression therapy has been identified as a risk factor for non-albicans candidemia.[21] In the present study, the rate of immunosuppression therapy was lower in elderly patients. This clinical factor was different from previous findings. In addition to immunosuppression therapy, other factors (eg, a history of gastrointestinal surgery and antifungal exposure) have been also reported as risk factors for non-albicans candidemia.[22] Neutropenia and immunosuppression therapy were previously identified as risk factors for death among patients

with candidemia.[8,23,24] However, these factors were not associated with a high mortality rate in our study. A meaningful statistics analysis could not be performed because of the insufficient number of patients, which was a limitation of this study.

The mortality rate of patients with a high APACHE II score was previously reported to be high.[8,10,24,25] In the present study, the APACHE II score was only obtained in 34 (45.3%) patients due to the lack of clinical data. Our result was consistent with these studies since non-survivors had a significantly higher score than that of survivors. The limitations of this study were the multivariate logistic regression analysis for death without APACHE II scores and small number of cases.

In conclusion, we identified two factors that correlated with death due to candidemia: advanced age and a failure to remove CVC. Physicians who treat candidemia need to consider removing CVC and pay attention to the general condition of patients, particularly elderly patients. The results of the present study provide a clearer understanding of the epidemiology of candidemia in Japan.

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Disclosure

There are no conflicts of interest associated with this study.

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