J Infect Chemother 25 (2019) 341–345

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Mortality and risk factor analysis for *Candida* blood stream infection: A multicenter study☆

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ARTICLE INFO

Article history:
Received 22 October 2018
Received in revised form
17 December 2018
Accepted 11 January 2019
Available online 2 February 2019

Keywords:
Community-acquired fungemia
Follow-up blood culture
Sequential organ failure assessment score
Aging
Multi-drug resistant organisms
Antifungal stewardship

ABSTRACT

Candida blood stream infection (candidemia) is severe systemic infection mainly develops after intensive medical cares. The mortality of candidemia is affected by the underlying conditions, causative agents and the initial management. We retrospectively analyzed mortality-related risk factors in cases of candidemia between April 2011 and March 2016 in five regional hospitals in Japan. We conducted bivariate and multivariate analysis of factors including causative *Candida* species, patients' predisposing conditions, and treatment strategies, such as empirically selected antifungal drug and time to appropriate antifungal treatment, to elucidate their effects on 30-day mortality. The study enrolled 289 cases of candidemia in adults. Overall 30-day mortality was 27.7%. Forty-nine cases (17.0%) were community-acquired. Bivariate analysis found advanced age, high Sequential Organ Failure Assessment (SOFA) score, and prior antibiotics use as risk factors for high mortality; however community-acquired candidemia, *C. parapsilosis* candidemia, obtaining follow-up blood culture, and empiric treatment with fluconazole were associated with low mortality. Logistic regression revealed age ≥65 years (adjusted odds ratio, 2.13) and sequential organ failure assessment (SOFA) score ≥6 (6.30) as risk factors for 30-day mortality. In contrast, obtaining follow-up blood culture (0.38) and empiric treatment with fluconazole (0.32) were found to be protective factors. The cases with candidemia in associated with advanced age and poor general health conditions should be closely monitored. Obtaining follow-up blood culture contributed to an improved prognosis.

1. Introduction

The number of *Candida* bloodstream infections (candidemia) has increased as a common sequela of intensive medical care, for example, central venous catheter (CVC) placement [1]. Candidemia accounts for 4.5% of positive clinical blood testing positive for infection [2]. Although infectious disease management and antifungal treatments have improved, the mortality rate of candidemia remains around 30% [3,4]. Mortality is higher for postoperative bloodstream infections due to *Candida* species than to bacterial organisms [5]. Contributing to the high morbidity associated with candidemia are factors including current health status such as

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA score, Sequential Organ Failure Assessment score; CVC, central venous catheter.

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https://doi.org/10.1016/j.jiac.2019.01.002
1341-321X/

diabetes mellitus, neutropenia, and severe systemic conditions [6,7]. In particular, advanced age is a leading risk factor for mortality in patients with candidemia [7,8], and the elderly population in Japan is growing dramatically due to the prolonged life expectancy of both sexes. In addition, trends regarding causative candida species have changed over time. In particular, the incidence of candidemia due to non-albicans *Candida* species including *C. glabrata*, *C. tropicalis*, and *C. krusei* reportedly is increasing and accompanied by high mortality [8,9], and the antifungal therapy selected should be modified accordingly in response [10]. Furthermore, about 11% of candidemia cases are community-acquired [11], and their characteristics are incompletely described. Therefore, we here studied the causative pathogens, predisposing conditions, and risk factors associated with candidemia in a rapidly aging society.

2. Material and methods

We retrospectively collected from the medical records of five regional and university hospitals in southern Kanagawa prefecture, Japan, all consecutive cases of candidemia that occurred in adults between April 2012 and March 2017. A case was defined when blood culture yielded at least one *Candida* species. Three pediatric cases (age, 0–1 year) were excluded from the study dataset, which then comprised 289 cases of candidemia in adults (age, ≥18 years). The 289 cases included in this study were collected from the following centers: Yokohama Municipal Citizen's Hospital (650 beds), 105 cases; Yokohama City University Hospital (672 beds), 76 cases; Yokohama City University Medical Center (726 beds), 57 cases; National Hospital Organization Yokohama Medical Center (500 beds), 30 cases; and Fujisawa City Hospital (536 beds), 21 cases. This study was approved by the ethics committee at each participating institution (approval numbers: 201611-03, B160900004, D1401020, F2016032, and 28-19, respectively).

The patients' predisposing conditions and clinical status at the time of onset of candidemia (the time when the blood culture was positive for *Candida*) were obtained from the medical records. Predisposing conditions evaluated included gender, age, admitting department, causative *Candida* species, presence of diabetes, corticosteroid use (≥1 week, regardless of dosage), presence of cancer, neutropenia (absolute neutrophil count <500/μL), intensive care unit (ICU) admission, and presence of a CVC at the time of disease onset. The highest Sequential Organ Failure Assessment (SOFA) score during hospitalization was recorded. When the blood culture was positive for bacteria in addition to *Candida* species, the case was defined as having concurrent bacteremia.

Data regarding clinical course and prognosis were collected; this information included antibiotic use before the onset of candidemia, selected empiric antifungal drug, antifungal drugs, and time to appropriate antifungal treatment. Cases consistent with the following conditions were defined as community-acquired: development of candidemia within 2 days of hospital admission or no history of admission during the 60 days prior to onset. Drug susceptibility testing was not performed in all cases. Instead, the appropriate drugs for treatment were defined according to the causative *Candida* species and the antifungal agents selected for use in this study. Therefore, the use of fluconazole to treat *C. albicans*, *C. parapsilosis*, and *C. tropicalis* candidemia and the use of micafungin, caspofungin, voriconazole, or liposomal amphotericin-B (L-AMB), regardless of the infecting *Candida* species, were considered appropriate. No cases of L-AMB-resistant *C. lusitaniae* candidemia were treated with L-AMB. Empiric therapy with a selected antifungal drug was initiated after recognition of the signs of candidemia.

Patients with a history of detection of methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase–producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, or multidrug-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, or *Clostridioides difficile*, regardless of infection or colonization, were categorized as colonized with multidrug-resistant microorganisms (MDRO).

Continuous data are reported as means and 95% confidence intervals (CIs) or medians and interquartile ranges (IQRs). Categorical data are presented as numbers and percentages. Data were analyzed by using two-tailed Mann–Whitney U-tests for comparisons of continuous variables between two groups and by Fisher's exact test for comparisons of categorical data. Log-rank testing was performed to compare survival rate analyses. Receiver–Operator Curve analysis was used to identify cut-off values for age and SOFA score in multivariate analysis. Multivariate regression logistic analyses were performed to investigate predictors of 30-day mortality, and adjustments were made for potential confounders, including age ≥65 years, *C. parapsilosis* fungemia, follow-up blood culture, SOFA score ≥6, prior antibiotic use, and empiric treatment with fluconazole; the results of the bivariate analysis indicated that the listed factors contributed strongly to 30-day mortality. Kaplan–Meier analysis was used to assess survival according to candida species. Statistical analyses were performed by using Toukei–Kaiseki for Mac version 2.0 (Esumi, Tokyo, Japan) and Prism 7 (GraphPad Software, San Diego, CA, USA). A *P* value of 0.05 or less was considered to indicate a statistically significant difference.

3. Results

3.1. Predisposing conditions and underlying risk factors

Demographic and clinical characteristics of the study population are shown in Table 1. The median age was 70.0 years, and 61.9% of patients were male. Of the 289 patients, 80 (27.7%) died within 30 days of onset of candidemia. *Candida albicans* was the most frequent causative agent (44.3%), followed by *C. parapsilosis* (25.3%), and *C. glabrata* (15.9%). Cases of *C. parapsilosis* candidemia were more numerous in the surviving group compared with the 30-day mortality group (28.7% vs 16.3%, $P = 0.024$). In addition, Kaplan–Meier analysis of survival relative to *Candida* species indicated that the survival rate was higher for *C. parapsilosis* candidemia compared with other species or mixed fungemia ($P = 0.044$) (Fig. 1). Of the 289 cases enrolled, 49 (17.0%) were community-acquired candidemia. The causative pathogens in cases of community-acquired candidemia were *C. albicans*, ($n = 17$); *C. parapsilosis*, ($n = 16$); *C. glabrata*, ($n = 13$), and undetermined *Candida* species ($n = 3$). Of these, 20 cases received home parenteral nutrition. The rate of community-acquired candidemia was found higher in the survived group compared with hospital-acquired candidemia (20.1% vs 8.7%, $P = 0.026$).

Regarding underlying conditions, the proportions of patients having diabetes, corticosteroid use, cancer, neutropenia, ICU admission, and CVC placement did not differ significantly between patients who survived and the 30-day mortality group. We were able to collect information regarding CVC removal or retention for only 138 cases among the 210 total cases of CVC placement; subgroup analysis of those 138 cases showed that the incidence of CVC removal did not differ between surviving patients and the 30-day mortality group (88.9% vs 87.2%, $P = 0.773$). Overall, the highest SOFA score (median, 6 [IQR, 3–10] vs 3 [1–5], $P < 0.001$) and the incidence of prior antibiotics use (76.3% vs 60.3%, $P = 0.013$) were higher for the 30-day mortality group than for patients who survived. The incidences of concurrent bacteremia and colonization with MDRO were similar between groups.

Follow-up blood culture after antifungal treatment was performed more frequently among patients who survived compared

Table 1
Characteristics, causative agents, and predisposing conditions of the study subjects.

	Total	Survived	Died within 30 days of onset	*P*
	(*n* = 289)	(*n* = 209)	(*n* = 80)	
Male – no. (%)	179 (61.9)	131 (62.7)	48 (60.0)	0.687
Age – years, median [IQR]	70.0 [58–77]	68 [54.5–77]	73.5 [64.3–78]	0.005*
Hospital-acquired	240 (83.0)	167 (79.9)	73 (91.3)	0.023*
Community-acquired	49 (17.0)	42 (20.1)	7 (8.7)	
Causative agent – no. (%)				
C. albicans	128 (44.3)	86 (41.1)	42 (52.5)	0.115[a]
C. parapsilosis	73 (25.3)	60 (28.7)	13 (16.3)	0.024*,[a]
C. glabrata	46 (15.9)	33 (15.8)	13 (16.3)	1.0[a]
C. tropicalis	14 (4.8)	9 (4.3)	5 (6.3)	
C. lusitaniae	5 (1.7)	4 (1.9)	1 (1.3)	
C. famata	5 (1.7)	3 (1.4)	2 (2.5)	
C. krusei	4 (1.4)	3 (1.4)	1 (1.3)	
C. guilliermondii	3 (1.0)	2 (1.0)	1 (1.3)	
C. pelliculosa	1 (0.3)	1 (0.5)		
Undetermined	6 (2.1)	5 (2.4)	1 (1.3)	
Mixed fungemia	4 (1.4)	3 (1.4)	1 (1.3)	
Underlying conditions and status – no. (%)				
Diabetes	47 (16.3)	31 (14.8)	16 (20.0)	0.290
Corticosteroid use	46 (15.9)	30 (14.4)	16 (20.0)	0.281
Cancer	93 (32.2)	65 (31.1)	28 (35.0)	0.574
Neutropenia	34 (11.8)	21 (10.0)	13 (16.3)	0.156
ICU admission	91 (31.5)	65 (31.1)	26 (32.5)	0.888
CVC placement	210 (72.7)	155 (74.2)	55 (68.8)	0.378
Highest SOFA score, median [IQR]	4 [1–6]	3 [1–5]	6 [3–10]	<0.001*
Prior antibiotics use	187 (62.5)	126 (60.3)	61 (76.3)	0.013*
Concurrent bacteremia	41 (14.2)	33 (15.8)	8 (10.0)	0.259
Colonized with MDRO	57 (19.7)	45 (21.5)	12 (15.0)	0.249
Follow-up blood culture	223 (77.2)	170 (81.3)	53 (66.3)	0.008*
(Persistent fungemia[c])	38 (17.0)	28 (16.5)	10 (18.9)	0.679
Empiric antifungal agents				
Fluconazole	47 (16.3)	41 (19.6)	6 (7.5)	0.012*
Voriconazole	2 (0.7)	1 (0.5)	1 (1.3)	
Micafungin or caspofungin	198 (68.5)	141 (67.5)	57 (71.3)	0.574
Amphotericin	13 (4.5)	8 (3.8)	5 (6.3)	0.358
Not treated	24 (8.3)	13 (6.2)	11 (13.8)	0.055
Unclear	5 (1.7)	5 (2.4)		
Time to appropriate antifungal therapy				
≤24 h	89 (30.8)	67 (32.1)	22 (27.5)	0.475[b]
≤48 h	75 (26.0)	56 (26.8)	19 (23.8)	0.178[b]
>48 h	90 (31.1)	64 (30.6)	26 (32.5)	
No antifungal drug treatment	24 (8.3)	13 (6.2)	11 (13.8)	0.056
Unclear	11 (3.8)	9 (4.3)	2 (2.5)	

IQR, interquartile range; CVC, central venous catheter; ICU, intensive care unit; MDRO, multidrug-resistant organisms; SOFA, Sequential Organ Failure Assessment.
* Statistically significant ($P \leq 0.05$).
[a] Compared with other *Candida* species.
[b] Compared with later time points or untreated.
[c] Among patients who were examined through follow-up blood culture.

with those who died within 30 days of candidemia onset (81.3% vs 66.3%, $P = 0.008$). Among the 223 cases for which follow-up blood culture was performed, 38 (17.0%) had persistent fungemia, which affected 16.5% of patients who survived and 18.9% of those in the 30-day mortality group ($P = 0.679$). Regarding treatment, candin agents (micafungin or caspofungin) were chosen most often for empiric antifungal treatment in our cohort (68.5%), followed by fluconazole (16.3%). Empiric treatment with fluconazole found more often among cases that survived than in the 30-day mortality group (19.6% vs 7.5%, $P = 0.012$). Time to appropriate antifungal therapy was ≤24 h for 30.8% of cases; >24 h to ≤48 h for 26.0%; and >48 h for 31.1%; 8.3% of cases never received appropriate antifungal therapy. The rate of time to appropriate antifungal therapy <24 h and <48 h were not significantly different between the survived and the 30-day mortality group.

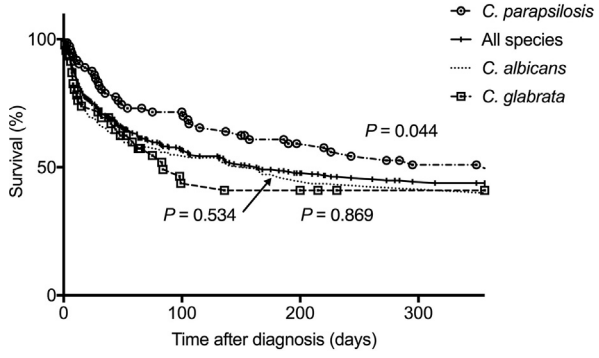

Fig. 1. Kaplan–Meier curves of survival rate according to *Candida* species compared with other species.

3.2. Multivariate logistic risk analysis for 30-day mortality

Because advanced age and highest SOFA score emerged as risk factors for 30-day mortality due to candidemia (Table 1), we performed Receiver–Operator Curve analysis of these factors. We found that SOFA score ≥6 (area under the curve = 0.750, $P < 0.001$) and age ≥65 years (area under the curve = 0.606, $P = 0.005$) were predictive of mortality. Multivariate logistic regression analysis

Table 2
Multivariate logistic regression analysis of the risk of 30-day mortality.

	Adjusted odds ratio	95% confidence interval	*P*
Age ≥65 years	2.13	1.10–4.11	0.024*
Community-onset candidemia	0.44	0.16–1.24	0.122
C. parapsilosis fungemia	0.63	0.29–1.34	0.230
Follow-up blood culture	0.38	0.19–0.74	0.005*
SOFA score ≥6	6.30	3.43–11.58	<0.001*
Prior antibiotics use	1.64	0.81–3.31	0.171
Empiric treatment with fluconazole	0.32	0.12–0.88	0.026*

SOFA, Sequential Organ Failure Assessment.
* Statistically significant ($P \leq 0.05$).

indicated that age ≥65 years (adjusted odds ratio [95% CI], 2.13 [1.10–4.11]), follow-up blood culture (0.38 [0.19–0.74]), SOFA score ≥6 (6.30 [3.43–11.58]), and empiric treatment with fluconazole (0.32 [0.12–0.88]) were significantly associated with 30-day mortality (Table 2).

4. Discussion

In this study, we investigated causative agents, predisposing conditions, and treatment strategies in cases of candidemia and analyzed risk factors for mortality in adult patients. Our findings revealed that advanced age (≥65 years), SOFA score ≥6, and previous antibiotics use were independent high-risk factors for 30-day mortality in adults with candidemia. In contrast, obtaining follow-up blood cultures and treatment with fluconazole were found to have protective roles. Prognosis was better for cases with *C. parapsilosis* candidemia any other *Candida* species. In support of our results, age ≥60 years and ≥65 years were predictors of high mortality in previous studies from Brazil and Australia [8,12]. In addition, poor overall health is strongly predictive of 30-day mortality due to candidemia. Given rapidly aging societies, we propose that age ≥65 is a more predictive risk factor for mortality in cases with candidemia.

The cases of community-acquired canidemia accounted 17.7% in this study, and had low mortality compared with nosocomial candidemia. Of the 49 cases of community-acquired candidemia, the 30-day mortality was 14.3%, significantly lower than hospital-acquired candidemia (30.4%). Twenty cases of community-acquired candidemia had received home parenteral nutrition because of gastrointestinal disease such as Crohn's disease and gastrointestinal cancer. In one report, 55% of community-acquired candidemia cases were associated with CVC placement [13]; in another, *Candida* species accounted for 9.6% of bloodstream infections in patients who received parenteral nutrition at home [14]. We considered that the high prevalence of *C. parapsilosis* contributed to the low mortality of community-acquired candidemia in our study. The lower mortality of *C. parapsilosis* candidemia has been reported in previous study, however the reason of low mortality was not clearly explained [15]. Patients who receive home parenteral nutrition should be monitored closely to prevent candidemia and other sequelae. Another predisposing condition in patients who developed community-acquired candidemia was gastrointestinal perforation; in our study, seven patients developed candidemia after gastrointestinal perforation. Prophylactic antifungal therapy is recommended for patients with gastrointestinal perforation [4]. The major predisposing condition in the twenty-two remaining cases of community-acquired candidemia was pneumonia (n = 5).

In earlier studies, high Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were widely used as predictors of high mortality in patients with candidemia [6,7,16]. Instead of APACHE II scores, we adopted SOFA scoring for the current study because it was easy to calculate, and a SOFA score of 6 or greater emerged as a strong predictor of high mortality.

Prompt appropriate antifungal therapy is crucial in the treatment of candidemia, and delayed empiric antifungal therapy has been reported as an independent risk factor for high mortality [17]. In previous studies, only 11%–32% of patients with candidemia received appropriate antifungal therapy [18,19]. Our study failed to demonstrate significant benefits due to shorter times to appropriate antifungal therapy, but follow-up blood culture emerged as a predictor of favorable prognosis. Because persistent fungemia and poor response to initial antifungal therapy are reported risk factors for high mortality [16,20], the current standard of care is to obtain follow-up blood cultures after treatment and to confirm *Candida*-negative results, to prevent disseminated fungal infections. Although early CVC removal improved prognosis in cases of CVC-related candidemia in a previous study [21], the incidence of CVC removal did not differ between surviving patients and the 30-day mortality group in our current study. Among our study population, 68.5% of patients were treated empirically by using candin agents (micafungin or caspofungin), and 16.3% received empiric fluconazole. We are unable to explain the protective role of empiric treatment with fluconazole regarding 30-day mortality in our patients. However, from the point of view of antifungal stewardship, we suggested the initial treatment with fluconazole was re-evaluated for patients who are not critically ill. In our study, the highest SOFA score was nonsignificantly higher in the patients who were treated with drugs other than fluconazole than in patients initially treated with fluconazole (4.4 vs 3.6, $P = 0.115$). Initial treatment with fluconazole generally is preferred in patients who are not considered critically ill. In a surveillance study from Japan, the rate of fluconazole-resistant *C. albicans* was 2.4% [3]. Fluconazole-resistant *C. albicans* has not yet been reported in Yokohama City University Hospital, one of the institutions participating in this study.

Our current study had several limitations. First, this study was retrospective in design. Second, we did not differentiate whether death was due to candidemia or to deterioration of the underlying disease, because determining the precise cause of death in critically ill patients can be difficult. In addition, the highest SOFA score might have changed owing to deterioration of the underlying disease rather than as a consequence of candidemia. Regardless of these limitations, our study successfully revealed disease characteristics and risk factors for mortality in patients with candidemia. We surmise that appropriate management of patients with candidemia will become increasingly important in rapidly aging populations.

5. Conclusions

Among our 289 adult patients, the overall 30-day mortality due to candidemia was 27.7%, and 17.0% of cases were community-

acquired. Advanced age (≥65 years) and SOFA score ≥6 emerged as strong predictors of 30-day mortality in patients with candidemia, whereas follow-up blood culture had protective role for low mortality.

Conflicts of interest

Hideaki Kato received grants from Shionogi & Company, Limited, and Merck & Co., Inc. Other co-authors have no conflict of interest to declare.

Ethical standards

This study was approved by the ethics committee at each participating institution.

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