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Original article

Terminal-stage prognostic analysis in candidemia

Takahiro Takuma*, Hisashi Shoji, Yoshihito Niki

Department of Medicine, Division of Clinical Infectious Diseases, School of Medicine, Showa University, Tokyo, Japan

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ABSTRACT

Background: Candidemia has an extremely high mortality rate but is not always the direct cause of death. Therefore, determining the effect of candidemia on death is extremely difficult.
Methods: We investigated prognostic factors in patients with culture-proven candidemia at 2 Japanese university teaching hospitals from April 2009 through May 2013. To examine the effects of comorbid conditions, the Charlson comorbidity index was determined, and patients were subjectively classified into 3 clinical prognostic stages (terminal [death expected within 1 month], semiterminal [death expected within 6 months], and nonterminal [expected to live more than 6 months]). The Cox proportional hazard model was used for univariate and multivariate analyses of factors possibly affecting survival.
Results: On univariate analysis, factors identified as associated with an increased mortality rate were: admission to an internal medicine department, *Candida glabrata*, immunosuppression, hypotension, hypoxemia, and a terminal prognostic stage. Factors associated with a decreased mortality rate were: serum albumin, endophthalmitis investigation, and nonterminal prognostic stage. The mortality rate was significantly related to the prognostic stage on multivariate analysis ($P < 0.0001$), was increased by age ($P = 0.0014$), and was decreased by a delayed start of antifungal therapy ($P = 0.0374$).
Conclusion: In contrast to earlier studies, the present study has found that later antifungal usage is associated with a decreased mortality rate in cases of candidemia. More important than candidemia in causing the deaths of patients with candidemia were the patients' background and comorbidity status. Therefore, rigorous methods should be used when investigating causes of death in terminally ill patients with candidemia.

1. Introduction

Candidemia is a severe complication in immunocompromised patients. Although candidemia has a mortality rate of 30%–60% [1–9], investigating mortality in candidemia can be complicated. One problem is that most patients have numerous severe comorbid conditions that can themselves be the cause of in-hospital deaths. Therefore, distinguishing deaths due to candidemia from deaths due to comorbidities is extremely difficult. In particular, controlling for comorbidities is difficult unless a study's sample size is extremely large.

Another problem when investigating mortality in candidemia is that many patients are terminally ill and are not generally candidates for aggressive therapy. However, assessing the effects of treatment can be difficult because these patients might receive best-supportive care, elements of aggressive therapy, or a combination of both.

Therefore, to investigate mortality in candidemia, in the present study we examined survival and prognostic factors in patients, including terminally ill patients, with culture-proven candidemia at 2 Japanese university teaching hospitals. To control for the effects of comorbid conditions on mortality, the Charlson comorbidity index [10] was determined for each patient, and patients were subjectively classified into 3 clinical prognostic stages.

2. Patients and methods

2.1. Study location and data collection

Data from April 2009 through May 2013 at Showa University Hospital and Showa University East Hospital in Tokyo, Japan, which

* Corresponding author. Department of Medicine, Division of Clinical Infectious Diseases, School of Medicine, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan. Tel.: +81 3 3784 8777; fax: +81 3 3784 8780.
E-mail address: takuma@med.showa-u.ac.jp (T. Takuma).

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have a total of 1014 beds, were retrospectively collected. Each year in these hospitals 6000–7000 blood cultures are performed. All blood culture results from April 2009 through May 2013 were reviewed, and if the results were positive for fungi, the medical records of the patients' were reviewed. If 2 or more blood cultures were positive for a single patient, the first positive culture was used so that the observation period would be as long as possible. Fortunately, different species of *Candida* were not detected at the same time during the study period; therefore, 1 *Candida* species was matched to each case of candidemia. Diagnoses of *Candida* infection were checked by reviewing the patients' records, and positive results likely due to contamination were excluded. Patients had too many severe comorbidities (Table 1) to control for; therefore, the Charlson comorbidity index [10] was used instead of examining the effect of each comorbidity separately. In brief, each comorbidity was categorized by disease (Table 1), and index points were then added from the Charlson comorbidity index.

2.2. Definitions

We identified *Candida* species by means of a culture identification kit for fungi (SYSMEX bioMérieux Co., Ltd.; Tokyo, Japan). Species of *Candida* other than *Candida albicans* or *Candida glabrata* were included in "other." Contamination was considered when only 1 of 2 or more bottles was positive for *Candida* without any focal signs or symptoms. Immunosuppression was considered to be present if patients were receiving immunosuppressive agents or anticancer drugs. Hypotension was defined as a systolic blood pressure less than 90 mm Hg or by hypotension requiring treatment with a vasopressor. Hypoxemia was defined by an oxygen saturation, measured with a pulse oximeter, of less than 90% or by a low oxygen saturation requiring treatment with supplemental oxygen.

The clinical prognostic stage was subjectively judged by a single physician. "Terminal" meant that the patient was expected to die within 1 month, "semiterminal" meant that the patient was expected to die within 6 months, and "nonterminal" meant that the patient was expected to be alive for more than 6 months. Although the clinical prognostic stage was judged through a review of medical records until the time a blood culture was positive for fungi, the judgment was made retrospectively and in a nonblinded manner. Therefore, the clinical prognostic stage was likely somewhat biased. The comorbidities were divided by these clinical prognostic stages (Table 1). The date of antifungal therapy was the interval between when a blood sample was obtained for culture and the start of antifungal therapy. The date of catheter removal was the interval between when a blood sample was obtained and catheter removal.

2.3. Cases description

To understand the differences between the findings of earlier studies [3,5,6] and those of the present study, which will be described later, we examined the relationship between hospital mortality and the date of antifungal therapy [3]. More detailed descriptions of the clinical course were added for patients for whom treatment was started on day 4 or later.

2.4. Statistical analysis

The software program JMP 10.0.2 (SAS Institute Inc., Cary, NC) was used for analyses. In both univariate and multivariate analyses, the Cox proportional hazard model was used for survival analyses. All factors of univariate analyses (Table 2) were included in multivariate analysis. Kaplan–Meier curves were also constructed to show the effects of clinical prognostic stage on outcome.

3. Results

During the study period, 136 blood cultures from 56 patients were positive for fungi. All fungi were *Candida* species. Because 5 cultures from 4 patients were believed to be positive because of contamination, the remaining 52 cases were analyzed. Of the cases of candidemia, 34 were from our university's internal medicine departments, including the departments of cardiovascular medicine (8 cases), respiratory medicine (7 cases), gastroenterological medicine (7 cases), pediatrics (4 cases), hematology (3 cases), oncology (2 cases), rheumatology (2 cases), and nephrology (1 case). Eighteen cases of candidemia were from surgical departments, which included the departments of digestive surgery (9 cases), cardiovascular surgery (3 cases), cerebral surgery (2 cases), urology (2 cases), otorhinolaryngology (1 case), and gynecology (1 case). Species of *Candida* other than *C. albicans* (22 cases) or *C. glabrata* (7 cases) were *Candida parapsilosis* (10 cases), *Candida*

Table 1
Major comorbidities present in multiple patients according to Charlson Comorbidity Index, divided by clinical prognostic stage.

Comorbidities	Index points	Cases by clinical prognostic stage		
		Terminal (23 patients)	Semiterminal (16 patients)	Nonterminal (13 patients)
Myocardial infarction	1	3	2	1
Congestive heart failure	1	4	4	1
Peripheral vascular disease	1	1	1	2
Cerebrovascular disease (without hemiplegia)	1	0	1	0
Hemiplegia	2	4	3	1
Dementia	1	1	4	0
Chronic pulmonary disease	1	7	3	0
Connective tissue disease	1	2	0	0
Ulcer disease	1	5	1	3
Mild liver disease	1	3	2	4
Moderate or severe liver disease	3	0	0	0
Diabetes (without end-organ damage)	1	3	3	4
Diabetes with end-organ damage	2	1	0	0
Moderate or severe renal disease	2	4	3	1
Any tumor (without metastasis)	2	2	3	2
Metastatic solid tumor	6	7	5	0
Leukemia	2	1	1	0
Lymphoma	2	1	0	0
Acquired immunodeficiency syndrome	6	0	0	0