Risk Factors for Mortality in Patients with Candidemia and the Usefulness of a Candida Score

In Ki Moon, Eun Jung Lee†, Hyo Chul Kang, Shi Nae Yu, Jee Wan Wee, Tae Hyong Kim, Eun-Joo Choo, Min Hyuk Jun and Se Yoon Park

Division of Infection Department of Internal Medicine, SoonChunHyang University Seoul Hospital

= Abstract =

Background: Although effective antifungal agents for the treatment of candidemia have recently been introduced, the mortality rate attributed to candidemia remains high (19~49%).

Objective: This study aimed at evaluating the risk factors for mortality in patients with candidemia and at assessing the usefulness of a Candida Score in these patients.

Methods: A cohort of patients with positive blood cultures for *Candida* species was retrospectively analyzed at Soonchunhyang University Hospital, a 750-bed teaching hospital, from May 2003 to February 2012. The Candida Score was calculated by assigning 1 point to any of total parenteral nutrition (TPN), surgery, or multifocal *Candida* species colonization, and 2 points to severe sepsis.

Results: Sixty patients (68.3% men; mean age (standard deviation [SD]), 61.8 [18.9] years) with blood cultures positive for *Candida* species were identified. Most patients had been admitted to an intensive care unit (48 [80%]), were receiving broad-spectrum antibiotics (37 [61.7%]), had TPN (29 [48.3%]), had diabetes mellitus (23 [38.3%]), and were receiving hemodialysis (10 [16.7%]). The mean (SD) Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 19.60 (8.8). Twenty-three patients (38.3%) had a Candida Score >2.5. The *Candida* species causing infection included *C. albicans* (41 [68.3%]), *C. tropicalis* (7 [11.7%]), *C. parapsilosis* (4 [6.7%]), *C. krusei* (3 [5%]), *C. glabrata* (3 [5%]), *C. guilliermondii* (1 [1.7%]), and *C. catenulata* (1 [1.7%]). Only 32 patients (53.3%) received adequate antifungal treatment. The candidemia-related mortality rate was 61.7% (n = 37 patients). Multivariate logistic regression analysis demonstrated that a high APACHE II score (adjusted odds ratio [aOR], 1.2; 95% confidence interval [95% CI], 1.0~1.3; $p = 0.01$), presence of a malignancy (aOR, 14.8; 95% CI, 2.5~88.0; $p = 0.003$), and treatment with an antifungal agent (aOR, 0.2; 95% CI, 0.0~1.0; $p = 0.048$) were associated with disease-related mortality.

Conclusion: The risk factors for mortality in patients with candidemia are a high APACHE II scores and presence of a malignancy. However, the sensitivity of the Candida Score was not high (38.3%). New methods to rapidly identify candidemia and avoid delays in treatment with appropriate antifungal therapy are needed. **[Korean J Med Mycol 2013; 18(3): 59-65]**

Key Words: Candidemia, Candida score, Antifungal therapy

Received: March 30, 2013, Revised: September 13, 2013, Accepted: September 16, 2013

†Corresponding author: Eun Jung Lee. Division of Infection Department of Internal Medicine, SoonChunHyang University Seoul Hospital, 140-743, Korea.
Tel: +82-2-709-9034, Fax: +82-2-795-3687, e-mail: shegets@schmc.ac.kr

INTRODUCTION

The incidence of invasive fungal infections is increasing, with infection by *Candida* species being the most common type of fungal infection (70~87%)[1]. In particular, there has been a 5- to 10-fold rise in nosocomial bloodstream infections (BSIs) caused by *Candida* species in the past 20 years, such that *Candida* BSIs are now the fourth leading cause of nosocomial BSIs in the United States[2,3]. Candidemia is associated with significant affects overall and cause-specific mortality, excessive morbidity, and prolongation of hospital stay[4~6]. Several studies have shown that the mortality rate of nosocomial candidemia is approximately 30~60% among patients admitted to intensive care units (ICUs)[7~9]. In Korea, the candidemia-related incidence and mortality rates among severe burn patients are 8.6% and >40%, respectively. In another study from 2009, Han et al found that the incidence and mortality rates of candidemia in ICU patients are 0.9% and 96%, respectively[10].

Delayed diagnosis and inappropriate therapy for candidemia results in increased mortality[11]. Early recognition of candidemia is important, but this is made difficult by the lack of specific signs and symptoms in patients and diagnostic tools to detect infections. Although newer, technologically advanced methods to detect candidemia have been developed, including 1,3-β-D-glucan assays, fungal DNA identification, *C. albicans* germ tube antibody tests, and mannan and anti-mannan antibody detection[1], the high cost, lack of experience among the hospital staff with these methods, and limited hospital resources prevent our hospital from these methods. Therefore, we used a Candida Score to detect candidemia infections[1,12]. While a Candida Score is useful, it is not frequently used in the clinical setting because routine cultures for *Candida* species are difficult to perform. In the present study, we evaluated the risk factors for mortality in patients with candidemia and the usefulness of a Candida Score in detecting infections.

MATERIALS AND METHODS

We conducted a retrospective study at a 750-bed tertiary medical center in the Republic of Korea. During a 9-year period (March 2003 to February 2012), all hospitalized patients with a positive blood culture for *Candida* species were analyzed.

Patient medical records were reviewed for demographic data, age, sex, and underlying diseases such as diabetes mellitus, chronic obstructive pulmonary disease, liver cirrhosis, chronic kidney disease, end-stage renal disease (ESRD; with the patient receiving hemodialysis), congestive heart failure, solid organ transplant, malignancy, human immunodeficiency virus infection, and neutropenia at the time of candidemia. We also obtained data regarding the patients' history of surgery, number of hospital days before candidemia infection and within 30 days of admission, use of total parenteral nutrition (TPN) and steroids, prior use of broad-spectrum antibiotics, prior ICU admission, use of mechanical ventilation, use of a Foley catheter and central catheter, combined bacteremia, *Candida* colonization, and the species identified, presumed source of *Candida* infection, Candida Scores, antifungal treatment (duration and agent), and outcomes. The severity of illness was based on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, presence of severe sepsis, white blood cell count, and albumin level.

Candidemia-related death was defined as the patient dying within 30 days of the initial blood samples testing positive for *Candida* species. The Candida Score was calculated by assigning 1 point for TPN, surgery, and multifocal *Candida* species colonization and 2 points for clinical severe sepsis (the variables were coded as 0 = absent and ≥1 =

present).

For comparing patients who died and those who survived, continuous variables were analyzed by Student's *t*-test for normally distributed variables and the Mann-Whitney U test for variables that were not normally distributed. The chi-square or Fisher's exact test was used to compare categorical variables. Values are expressed as the mean (SD) (continuous variables) or as a percentage of the group from which they were derived (categorical variables). Univariate and multivariate analyses were performed with SPSS, version 17.0 (SPSS, Chicago, Illinois, USA). *P* values less than or equal to 0.05 were considered significant.

RESULTS

1. Patient demographics

During the study period, a total of 60 patients with candidemia were included for analysis. The mean (SD) age of the patients was 61.8 (18.9) years and the mean (SD) APACHE II score was 19.6 (8.8). Forty-one patients (68.3%) were men, 23 patients (38.3%) had diabetes mellitus, 10 patients (16.7%) had ESRD and were receiving hemodialysis, 25 patients (41.7%) had an underlying malignancy, and 9 patients (15.0%) had neutropenia.

At the time of hospital admission for candidemia infection, 19 patients (31.7%) had a history of surgery, 29 patients (48.3%) had been given TPN, 37 patients (61.7%) were administered broad-spectrum antibiotics, 24 patients (40%) had mechanical ventilation, 48 patients (80%) had been admitted to an ICU, and 42 patients (70%) had a central catheter. Thirty-six patients (60%) had severe sepsis and 22 patients (36.7%) had combined bacteremia. Nine patients (15%) had blood cultures positive for *Candida* species colonization. The Candida Score was measured in all patients, and showed that 23 patients (38.3%) had

Table 1. Demographics of patients with candidemia

	Total (n = 60)
Age, mean years (SD)	61.8 (18.9)
Male sex (%)	41 (68.3)
Disease related mortality (%)	37 (61.7)
Underlying disease (no, %)	
Diabetes mellitus	23 (38.3)
COPD	3 (5)
Liver cirrhosis	5 (8.3)
Chronic kidney disease	5 (8.3)
Congestive heart failure	1 (1.7)
Solid transplantation	1 (1.7)
ESRD on hemodialysis	10 (16.7)
Malignancy	25 (41.7)
Neutropenia	9 (15.0)
HIV infection	0 (0)
Risk factor (no, %)	
Operation history	19 (31.7)
Total parenteral nutrition	29 (48.3)
Broad spectrum antibiotics	37 (61.7)
ICU admission	48 (80.0)
Mechanical ventilation	24 (40.0)
Foley catheter	34 (56.7)
Central catheter	42 (70.0)
Steroid use	5 (8.3)
Candida colonization	9 (15.0)
Severity of illness	
APACHE II, mean (SD)	19.6 (8.8)
Severe sepsis (%)	36 (60.0)
Albumin g/dL, median (range)	2.8 (1.7 to 4.1)
WBC $10^3/\mu L$, median (range)	9,900 (100 to 33,800)
Combined bacteremia (%)	22 (36.7)
No. of patients (%) with a:	
Candida Score value >2.5	23 (38.3)
Antifungal treatment	
Use (no, %)	32 (53.3)
Timing (from event day)	3.2 (-11 to 19)
Duration (days)	14.0 (1 to 39)

a Candida Score of >2.5 (Table 1).

Among the *Candida* species identified, *C. albicans* was most commonly detected pathogen (41 [68.3%]), followed by *C. tropicalis* (7 [11.7%]), *C. parapsilosis* (4 [6.7%]), *C. krusei* and *C. glabrata* (3 [5%] for both), and *C. catenulata* and *C. guilliermondii* (1 [1.7%] for both) (Table 2). Thirty-two patients (53.3%) received antifungal treatment; the mean (SD) number of days between the start of treatment and candidemia infection was 3.2 (5.6) days (range, 11 to 19 days), and the mean (SD) duration of treatment was 14.0 (9.8) days (range, 1~39 days). The most common antifungal treatment was fluconazole (21 [35%] of 60 patients).

Table 2. *Candida* species identified in the blood cultures and the candidemia-related mortality rate

Candida species	No (%)	Mortality rate (%)
Candida albicans	41 (68.3)	58.5
Candida tropicalis	7 (11.7)	71.4
Candida parapsilosis	4 (6.7)	25
Candida krusei	3 (5.0)	100
Candida glabrata	3 (5.0)	100
Candida catenulata	1 (1.7)	100
Candida guilliermondii	1 (1.7)	0

2. Risk factors for mortality

The disease-related mortality rate was 61.7% (n = 37). Univariate analysis showed that the risk factors for mortality included presence of a malignancy, receiving mechanical ventilation, having a

Table 3. Univariate analysis for risk factors of candidemia-related deaths

	Survivors (n = 23)	Non-survivors (n = 37)	*P*-value
Mean age, years (SD)	57.5 (24.9)	64.5 (13.6)	0.22
Male sex	15 (65.2)	26 (70.3)	0.68
Underlying disease			
Diabetes mellitus	10 (43.5)	13 (35.1)	0.52
ESRD on dialysis	5 (21.7)	5 (13.5)	0.49
Malignancy	6 (26.1)	19 (51.4)	0.05
Liver cirrhosis	1 (4.3)	4 (10.8)	0.64
Risk factor			
ICU admission	17 (73.9)	31 (83.8)	0.51
Operation history	8 (34.8)	11 (29.7)	0.68
Total parenteral nutrition	8 (34.8)	21 (56.8)	0.10
Mechanical ventilation	6 (26.1)	18 (48.6)	0.08
Central catheter	13 (56.5)	29 (78.4)	0.07
Severity of illness			
Mean APACHE II (SD)	14.9 (6.5)	22.5 (8.9)	0.001
Severe sepsis	10 (43.5)	26 (70.3)	0.04
Combined bacteremia	5 (21.7)	17 (45.9)	0.06
Use of antifungal agent	17 (73.9)	15 (40.5)	0.01

Table 4. Multivariate analysis for risk factors of candidemia-related deaths

Risk factor	Adjusted relative risk (95% CI)	*P*-value
APACHE II score	1.2 (1.0~1.3)	0.01
Malignancy	14.8 (2.5~88.0)	0.003
Received antifungal agent	0.2 (0.0~1.0)	0.05

central venous catheter, having a high APACHE II score, and having severe sepsis (Table 3). Multivariate analysis showed that a high APACHE II score (adjusted odds ratio [aOR], 1.16; 95% confidence interval [95% CI], 1.05~1.29; p = 0.01) and having a malignancy (aOR, 14.8; 95% CI, 2.59~88.0; p = 0.003) were associated with disease-related mortality. In addition, patients who survived received more antifungal treatment than patients who died (aOR, 0.2; 95% CI, 0.0~1.0; p = 0.05) (Table 4).

DISCUSSION

In 2006, Garey et al found that the time from the onset of candidemia to the initiation of fluconazole therapy had an impact on mortality rates in patients with candidemia, with lowest mortality rates seen in patients who started therapy on day 0 (n = 14 patients [15%]), followed by patients who started therapy on day 1 (n = 9 [24%]), day 2 (n = 12 [37%]), and day ≥3 (n = 12 [41%])[11]. Another study examining the effects of delayed treatment found that deferment of treatment for >12 hours was an independent predictor of hospital mortality rate[12]. In our study, patients who survived had started antifungal agents an average of almost 2 days earlier than those who died, but this was not a significant finding. Early detection of a candidemia infection can result in early initiation of empirical antifungal treatment. Newer diagnostic methods for detecting candidemia have been developed (e.g., 1,3-β-D-glucan assays, fungal DNA identification, *C. albicans* germ tube antibody, and mannan and anti-mannan antibody tests)[1], but these methods are not yet intended for general use.

In 2006, Leon et al suggested using a Candida Score to detect candidemia and found a sensitivity rate of 81.4% and a false-positive rate of 25.9%. The cutoff value was a score of >2.5, with sepsis, multifocal *Candida* colonization, parenteral nutrition, and surgery contributing to the score[13]. Leon et al showed that, in patients with a Candida Score of <3 who were not receiving antifungal treatment, the rate of invasive candidiasis was <5%; therefore, invasive candidiasis was highly improbable if patients had a Candida Score of <314. In our study, while the patients had several risk factors for candidemia, the sensitivity of the Candida Score was only 38.3% (cutoff value >2.5). This may be due to the retrospective nature of the study and the fact that patients were not routinely tested for *Candida* colonization. Had the patients been routinely tested for *Candida* colonization, the sensitivity of the Candida Score may have been higher. However, a routine *Candida* colonization test may be difficult in a setting with limited resources. The development of an easier prediction tool for candidemia is therefore needed.

Earlier studies have shown an overall candidemia mortality rate of approximately 60% among adults[15~17], and the mortality rate attributable to candidemia has been reported to be as high as 38%[17]. Recent studies have suggested lower overall and attributable candidemia mortality rates[4,18]. The risk factors for death caused by candidemia are known to be a high APACHE II score, presence of other bacteremia, sepsis, comorbid conditions (like malignancy), *Candida* species (*C. glabrata* and *C. krusei*), and catheter insertion, as well as other factors. In our study, the disease-related mortality rate was 61.7%, which was associated with patients

having combined bacteremia (but this was not found to be significant in statistical analysis) and failure to detect invasive candidiasis early which tended to delay the initiation empirical treatment with antifungal agents.

Specifically, the mortality rate of patients with candidemia caused by *C. glabrata* (n = 3), *C. krusei* (n = 3), and *C. catenulate* (n = 1) was 100%. Only 1 patient with *C. glabrata* infection received fluconazole, and 2 patients with *C. krusei* infection received amphotericin B and caspofungin, respectively. First of all, *C. glabrata* and *C. krusei* infection were known that mortality is high and they have resistance for antifungal agents[19]. However, these patients received therapies more than 1 week after the blood culture, at which point they already had high APACHE II scores. In addition, we could not decide its appropriateness because of lack information regarding the susceptibility to antifungal agents in our center.

This study determined that the risk factors for disease-related death were having a higher APACHE II score and presence of a malignancy. Moreover, treatment with antifungal agents decreased the mortality rate. However, this study has several limitations. First, data was collected from a single center, resulting in a limited sample size that may reflect regional infection patterns. Second, patients were evaluated retrospectively, meaning that the results may have been influenced by reviewer bias. Third, routine culture testing for all patients with candidemia was not performed.

In conclusion, the Candida Score used in our study was not found to be useful because its sensitivity was not high (38.3%). The risk factors for mortality in patients with candidemia are a high APACHE II score and presence of a malignancy. Novel, easy-to-implement, and low-cost methods to rapidly identify candidemia are needed to promptly commence antifungal therapy and improve the mortality rate for patients with candidemia. Especially in a limited resource setting, clinicians should consider the possibility of candidemia in critically ill patients: in suspected cases. repeated blood culture and empirical antifungal therapy are recommended. If possible, new non-culture-based microbiological tools such as *C. albicans* germ tube antibody detection or PCR techniques can be used to detect infection.

REFERENCES

1. Peman J, Zaragoza R. Current diagnostic approaches to invasive candidiasis in critical care settings. Mycoses 2010;53:424-433
2. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309-317
3. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 1999;29:239-244
4. Pappas PG, Rex JH, Lee J, Hamill RJ, Larsen RA, Powderly W, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis 2003;37:634-643
5. Nucci M, Silveira MI, Spector N, Silveira F, Velasco E, Martins CA, et al. Fungemia in cancer patients in Brazil: predominance of non-albicans species. Mycopathologia 1998;141:65-68
6. Wenzel RP. Nosocomial candidemia: risk factors and attributable mortality. Clin Infect Dis 1995;20:1531 -1534
7. Blot S, Vandewoude K, Hoste E, Poelaert J, Colardyn F. Outcome in critically ill patients with candidal fungaemia: *Candida albicans* vs. *Candida glabrata*. J Hosp Infect 2001;47:308-313
8. Cornwell EE, 3rd, Belzberg H, Offne TV, Dougherty WR, Morales IR, Asensio J, et al. The pattern of

fungal infections in critically ill surgical patients. Am Surg 1995;61:847-850

9. Voss A, le Noble JL, Verduyn Lunel FM, Foudraine NA, Meis JF. Candidemia in intensive care unit patients: risk factors for mortality. Infection 1997; 25:8-11
10. Han SS, Yim JJ, Yoo CG, Kim YW, Han SK, Shim YS, et al. Clinical characteristics and risk factors for nosocomial candidemia in medical intensive care units: experience in a single hospital in Korea for 6.6 years. J Korean Med Sci 2010;25:671-676
11. Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis 2006;43: 25-31
12. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother 2005;49:3640-3645
13. Leon C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-Lerma F, et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization. Crit Care Med 2006;34: 730-737.
14. Leon C, Ruiz-Santana S, Saavedra P, Galvan B, Blanco A, Castro C, et al. Usefulness of the "Candida score" for discriminating between *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. Crit Care Med 2009;37:1624-1633
15. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis 1992;15:414-421
16. Komshian SV, Uwaydah AK, Sobel JD, Crane LR. Fungemia caused by *Candida* species and Torulopsis glabrata in the hospitalized patient: frequency, characteristics, and evaluation of factors influencing outcome. Rev Infect Dis 1989;11:379-390
17. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia. The attributable mortality and excess length of stay. Arch Intern Med 1988;148:2642-2645
18. Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. Clin Infect Dis 1998;27:781 -788
19. Chae MJ, Song JW, Shin JH, Lee JS, Kim SH, Shin MG, et al. Comparison of real time quantitative PCR with northern hybridization for quantification of CgCDR1 and CgCDR2 gene expression in *Candida glabrata*. Kor J Med Mycol 2008;13:43-52