ORIGINAL ARTICLE

Epidemiological Study on *Candida* Species in Patients with Cancer in the Intensive Care Unit

Young-ju Choi[a], Byeongyeo Lee[a], Sun-A Park[b]

[a]Infection Control Unit, National Cancer Center, Goyang, Korea
[b]Division of Nursing Science, University of Suwon, Hwaseong, Korea

Objectives: Although cancer survival rates have increased, serious infection complications can arise in cancer patients. *Candida* can occur in various tissues and has significant effects on the prognosis of patients with cancer. Thus, we conducted an epidemiological study on *Candida* infections in patients with cancer admitted to the intensive care unit.
Methods: A retrospective study was conducted in adult patients with cancer admitted to the intensive care unit between January 1, 2013, and December 31, 2015. *Candida* infection status and predictive factors for mortality were examined in 634 patients.
Results: The predictive factors for mortality included the use of steroids, use of a central venous catheter or mechanical ventilator, and identification of *Candida* in the blood. Patients who stayed in the surgical and intensive care unit for more than 7 days had a lower risk of death than that in those with shorter days.
Conclusion: The present study shows that invasive procedures, bloodstream infections, and the use of steroids increase the risk of mortality in *Candida*-infected patients with cancer. To improve the quality of life and reduce mortality, further studies are needed on the factors affecting the risk of mortality associated with *Candida* infection.

Key Words: neoplasms, *Candida*, infection, intensive care units

INTRODUCTION

Candida is recognized as an important microorganism in healthcare-related infections [1], which have a rising incidence due to increases in extensive antibiotic administration, invasive treatments, and immunosuppressant use [2]. *Candida* infections are associated with a higher risk of mortality than non-fungal infections; the mortality rate can be as high as 90%, depending on associated risk factors [3]. In the United States, candidemia accounts for 8% of pathogenic bloodstream infection cases (15% in the intensive care unit [ICU]), and *Candida* is the fourth most commonly identified causative organism in bloodstream infections [4].

Cancer is a general risk factor for *Candida* infection [5]. Although the survival rates in patients with cancer have increased due to the availability of radiation, chemotherapy, and bone marrow transplant treatments, complications of serious infection can result from these treatments or from the effects of the disease itself. The acquisition of resistance in microorganisms with high sensitivity to previous antibiotic use in patients with cancer has been reported; due to a prolonged period with a decreased level of neutrophils and the use of extensive antibiotics, there is a high risk of fungal infection by *Candida* or *Aspergillus* in this population [6]. A na-

tionwide cohort study reported that *Candida* infection increases the risk of cancer [7] and can cause pneumonia in patients with lung cancer [8]. Furthermore, *Candida* infections occur in various tissues [9] and have a significant effect on prognosis. Thus, the study of *Candida* infections in patients with cancer is essential, particularly in terms of risk factors for mortality. The risk of mortality has been reported to increase in patients with cancer in the following situations: the patient is infected with *Candida albicans*, antifungal drugs are not used, the patient is admitted to the ICU, and the patient has an acute respiratory problem [6]. Furthermore, the risk of mortality in patients with *Candida* infection in the ICU has been reported to increase when antifungal drugs or mechanical ventilation are used [10].

Candida infections in the ICU increase mortality by 90% in patients with septic shock, and appropriate treatment and prevention in the ICU have a positive impact on patient outcomes [11]. Thus, we conducted an epidemiological study on the incidence of *Candida* infection in patients with cancer admitted to the ICU and evaluated the risk factors for mortality. The results of the present study provide important basic data for managing *Candida* infections in patients with cancer.

MATERIALS AND METHODS

1. Materials

An epidemiological study was conducted in patients with cancer admitted to the ICU at National Cancer Center (Goyang, Korea) between January 1, 2013, and December 31, 2015. A total of 634 patients with cancer aged over 19 years were included.

Cancer was diagnosed in patients whose *Candida* was detected at least once while in the ICU, and conditions other than age were not considered in the selection criteria. The electronic medical records were examined using a structured questionnaire administered by one researcher. This study was conducted with approval from the institutional review board of National Cancer Center (NCC2016-0126).

2. Definitions

Yeast is a heterogeneous group of fungi that looks homogenous on the surface. Generally, genera are determined by morphology and species is determined by biochemical assimilation. *C. albicans* was identified by a positive germ tube test and non-*C. albicans* (NCA) by a negative germ tube test. Healthcare-associated infection (HAI) was defined according to the Center for Disease Control and Prevention [12]. Mortality was defined as a death occurring during the hospitalization period.

Data regarding the prescribed use of antifungals, steroids, and antibiotics during the ICU admission period were collected, but dosage was not considered.

3. Statistical analysis

Statistical analyses were performed using SPSS version 21.0 software (IBM Co., Armonk, NY, USA). The frequency of *Candida* occurrence was determined. Associations between the examined variables and mortality risk in *Candida*-infected patients with cancer were evaluated using chi-square tests. In addition, a logistic regression analysis was performed to evaluate the risk factors predicting mortality in *Candida*-infected patients with cancer.

RESULTS

1. Incidence rate of *Candida* infection

During the 3-year study period, 634 cases of *Candida* infections occurred among the 17,797 patients who entered the ICU with a cancer diagnosis. Among them, *C. albicans* accounted for 544 cases (85.8%) and 90 cases (14.2%) were classified as NCA.

2. Factors affecting mortality risk in *Candida*-infected patients

The following factors were associated with a higher mortality risk: HAI (odds ratio [OR], 3.162; $p < 0.05$), shorter hospital stay (< 7 days; OR, 0.307; $p < 0.01$), no surgical treatment (OR, 0.149; $p < 0.01$), chemotherapy (OR, 1.577; $p < 0.05$), use of antifungal drugs or steroids (OR, 1.566 and 1.699, respectively; $p < 0.05$), central venous catheter use (OR, 2.64; $p < 0.01$), mechanical ventilator use (OR, 3.592; $p < 0.01$), bloodstream infections (OR, 2.246; $p < 0.01$), and NCA infections (OR, 1.582; $p < 0.05$). Sex, age, cancer type, and the use of antibiotics were not associated with mortality risk (Table 1).

3. Predictive factors for the risk of mortality in *Candida*-infected patients

Factors significantly associated with mortality risk in the univariate analyses were evaluated in a logistic regression analysis (Table 2). Hospital stays of 7 days or longer and surgery were found to significantly reduce the risk of mortality ($p < 0.01$), while the use of steroids ($p < 0.05$), central lines ($p < 0.01$), and mechanical ventilators ($p < 0.01$) and the identification of *Candida* in blood ($p < 0.01$) were found to significantly increase the risk of mortality.

Table 1. Association between clinical/patient factors and mortality in *Candida*-infected patients with cancer

Variable		Survived (n = 385)	Expired (n = 249)	OR (95% CI)	*p*-value
HAI	Yes	4 (33.3)	8 (66.7)	3.162 (0.942–10.614)	0.05*
	No	381 (61.3)	241 (38.7)		
Sex	Male	285 (61.7)	177 (38.3)	0.863 (0.604–1.232)	0.416
	Female	100 (58.1)	72 (41.9)		
Age (y)	< 65	209 (58.4)	149 (41.6)	0.797 (0.577–1.101)	0.168
	≥ 65	176 (63.8)	100 (36.2)		
Cancer type	Solid	343 (61.9)	211 (38.1)	1.471 (0.918–2.356)	0.107
	Hematology	42 (52.5)	38 (47.5)		
Length of hospital stay (d)	< 7	9 (33.3)	18 (66.7)	0.307 (0.136–0.695)	0.003**
	≥ 7	376 (61.9)	231 (38.1)		
Surgery	Yes	226 (70.8)	93 (29.2)	0.419 (0.302–0.582)	0.000**
	No	159 (50.5)	156 (49.5)		
Chemotherapy	Yes	81 (52.6)	73 (47.4)	1.557 (1.079–2.246)	0.018*
	No	304 (63.3)	176 (36.7)		
Antifungal drug use	Yes	142 (54.4)	119 (45.6)	1.566 (1.133–2.165)	0.006**
	No	243 (65.1)	130 (34.9)		
Steroid use	Yes	132 (53.0)	117 (47.0)	1.699 (1.226–2.353)	0.001**
	No	253 (65.7)	132 (34.3)		
Antibiotic use	Yes	379 (60.7)	245 (39.3)	0.97 (0.271–3.471)	0.962
	No	6 (60.0)	4 (40.0)		
Central line	Yes	126 (47.4)	140 (52.6)	2.465 (1.901–3.667)	0.000**
	No	259 (70.4)	109 (29.6)		
Mechanical ventilator	Yes	182 (48.9)	190 (51.1)	3.596 (2.521–5.118)	0.000**
	No	203 (77.5)	59 (22.5)		
Specimen	Blood	19 (42.2)	56 (57.8)	2.246 (1.215–4.152)	0.008**
	Other	366 (62.1)	223 (37.9)		
Candida species	*Candida albicans*	339 (62.3)	205 (37.7)	1.582 (1.010–2.476)	0.044*
	NCA	46 (51.1)	44 (48.9)		

Values are presented as number (%) or OR (95% CI).
HAI, healthcare-associated infection; OR, odds ratio; CI, confidence interval; NCA, non-*Candida albicans*.
*$p < 0.05$, **$p < 0.01$.

DISCUSSION

The present study evaluated the incidence of *Candida* infection in patients with cancer and factors associated with the risk of mortality in *Candida*-infected patients with cancer. We identified 634 cases of infection with *Candida* species, 75 of which involved bloodstream infections, among the 17,797 patients admitted to the ICU during the study period. This rate is relatively low compared with that reported in previous studies [2,6]. However, the proportion of *C. albicans* infections relative to NCA infections was 85.8%, which is higher than previously reported proportions

of 48.8% [6] and 74% [10].

In the present study, HAIs were significantly associated with an increased risk of mortality in *Candida*-infected patients with cancer, in contrast to a previous study that did not find a significant association [6]. Consistent with previous studies, sex and age were not associated with mortality risk in *Candida*-infected patients with cancer [6,10]. Although the present study did not find a difference in the risk of mortality between patients with hematology and those with solid tumors, a previous study reported that the mortality rate was higher in the presence of leukemia [13]. In terms of the length of the hospital stay, patients with a stay

Table 2. Factors predicting mortality in *Candida*-infected patients with cancer

Variable	B	Wald	OR	*p*-value	95% CI
HAI	0.385	0.356	1.469	0.551	0.415–5.196
Length of hospital stay	−1.273	7.912	0.28	0.005**	0.115–0.68
Surgery	−0.46	5.781	0.631	0.016*	0.434–0.918
Antifungal drugs	0.086	0.19	1.09	0.663	0.74–1.607
Steroids	0.386	4.248	1.471	0.039*	1.019–2.124
Chemotherapy	0.291	1.892	1.338	0.169	0.884–2.025
Central Line	0.566	9.105	1.761	0.003**	1.219–2.543
Mechanical ventilator	0.872	18.351	2.391	0.000**	1.605–3.563
Specimen (blood)	0.9	6.762	2.46	0.009**	1.248–4.849
Candida species	0.135	0.273	1.144	0.601	0.69–1.898

HAI, healthcare-associated infection; OR, odds ratio; CI, confidence interval.
*$p < 0.05$, **$p < 0.01$.

of 7 days or longer had a lower risk of mortality. In contrast, a previous study reported that the risk of mortality increased with longer hospital stays [14]. In the present study, the risk of mortality decreased when *Candida*-infected patients underwent surgery as a cancer treatment, while the risk of mortality increased when the patients underwent chemotherapy. A previous study comparing surgical patients and chemotherapy patients reported that patients receiving chemotherapy had a higher mortality rate (20% vs. 7.7%). In the present study, the risk of mortality increased with the use of antifungal drugs and steroids. However, a previous study reported an increased risk of mortality when antifungal drugs were not used [6], and another study reported an increased risk of mortality upon exposure to steroids [13]. In the present study, the use of antibiotics did not affect the risk of mortality; however, previous studies have reported that the risk increased with the use of broad-spectrum antimicrobials [6,14,15]. Further studies are required to resolve these inconsistencies.

Although the present study has a number of inconsistencies with previous studies, some of the results are consistent. In the present study, the risk of mortality increased with the use of a central line or mechanical ventilator, consistent with previous study results [16]. Also consistent with previous studies [17], the risk of mortality was higher when *Candida* was identified in the blood. Furthermore, cases with NCA infection had a higher risk of mortality than that in cases with *C. albicans* infection, consistent with numerous previous studies [18–20].

The results of the logistic regression analysis showed that patients who stayed more than 7 days in the ICU had a reduced risk of mortality. We interpreted that this was dependent on the characteristics of the patient. Patients admitted to the clinic's ICU for surgery often showed a relatively shorter duration of the disease; however, the same was not observed for patients undergoing chemotherapy.

In addition, a number of patients are admitted to the ICU right before death. The factors found to significantly increase the risk of mortality included the use of steroids, central lines, and mechanical ventilators as well as the identification of *Candida* in the blood. These results are the same as those in previous studies [16,17].

The present study was conducted in cancer patients admitted to the ICU who had a high risk of *Candida* infection according to previous studies. Therefore, the results may be limited in their generalizability. The present study results show that invasive procedures, bloodstream infections, and the use of steroids increase the risk of mortality in *Candida*-infected patients with cancer. The study results suggest that reducing the use of invasive procedures and preventing bloodstream infections in patients with cancer in the ICU could reduce mortality. Prevention of bloodstream infection by *Candida* is very important when considering that the prognosis of candidiasis-induced bloodstream infection is worse than that for other strains [21]. To reduce the mortality rate of patients with cancer, additional studies designed to prevent *Candida* and bloodstream infections are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

REFERENCES

1. Montagna MT, Caggiano G, Lovero G, et al. Epidemiology of invasive fungal infections in the intensive care unit: results of a multicenter Italian survey (AURORA Project). Infection 2013;41:645-53. https://doi.org/10.1007/s15010-013-0432-0

2. Ding X, Yan D, Sun W, et al. Epidemiology and risk factors for nosocomial Non-Candida albicans candidemia in adult patients at a tertiary care hospital in North China. Med Mycol 2015;53:684-90. https://doi.org/10.1093/mmy/myv060

3. De Rosa FG, Corcione S, Montrucchio G, et al. Appropriate treatment of invasive candidiasis in ICU: timing, colonization index, Candida score & biomarkers, towards de-escalation? Turk J Anaesthesiol Reanim 2016;44:279-82. https://doi.org/10.5152/TJAR.2016.0011

4. Diekema D, Arbefeville S, Boyken L, et al. The changing epidemiology of healthcare-associated candidemia over three decades. Diagn Microbiol Infect Dis 2012;73:45-8. https://doi.org/10.1016/j.diagmicrobio.2012.02.001

5. Zaoutis TE, Argon J, Chu J, et al. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis 2005;41:1232-9. https://doi.org/10.1086/496922

6. Tang HJ, Liu WL, Lin HL, et al. Epidemiology and prognostic factors of candidemia in cancer patients. PLoS One 2014;9:e99103. https://doi.org/10.1371/journal.pone.0099103

7. Nørgaard M, Thomsen RW, Farkas DK, et al. Candida infection and cancer risk: a Danish nationwide cohort study. Eur J Intern Med 2013;24:451-5. https://doi.org/10.1016/j.ejim.2013.02.017

8. Park SA, Cho SS, Kwak GJ. Factors influencing ventilator-associated pneumonia in cancer patients. Asian Pac J Cancer Prev 2014;15:5787-91. https://doi.org/10.7314/APJCP.2014.15.14.5787

9. Safdar A, Chaturvedi V, Cross EW, et al. Prospective study of Candida species in patients at a comprehensive cancer center. Antimicrob Agents Chemother 2001;45:2129-33. https://doi.org/10.1128/AAC.45.7.2129-2133.2001

10. Giri S, Kindo AJ, Kalyani J. Candidemia in intensive care unit patients: a one year study from a tertiary care center in South India. J Postgrad Med 2013;59:190-5. https://doi.org/10.4103/0022-3859.118036

11. Bassetti M, Righi E, Ansaldi F, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. Intensive Care Med 2014;40:839-45. https://doi.org/10.1007/s00134-014-3310-z

12. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309-32. https://doi.org/10.1016/j.ajic.2008.03.002

13. Jung DS, Farmakiotis D, Jiang Y, et al. Uncommon Candida species fungemia among cancer patients, Houston, Texas, USA. Emerg Infect Dis 2015;21:1942-50. https://doi.org/10.3201/eid2111.150404

14. Sahni V, Agarwal SK, Singh NP, et al. Candidemia--an under-recognized nosocomial infection in Indian hospitals. J Assoc Physicians India 2005;53:607-11.

15. Kumar CP, Sundararajan T, Menon T, et al. Candidosis in children with onco-hematological diseases in Chennai, South India. Jpn J Infect Dis 2005;58:218-21.

16. Xess I, Jain N, Hasan F, et al. Epidemiology of candidemia in a tertiary care centre of north India: 5-year study. Infection 2007;35:256-9. https://doi.org/10.1007/s15010-007-6144-6

17. Lee KS. Epidemiological study on fungal colonization and infections in critically ill patients in the Northern part of Gyeonggido [MS thesis]. Seoul: Yonsei University Graduate School; 2007.

18. Cornely OA, Gachot B, Akan H, et al. Epidemiology and outcome of fungemia in a cancer cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031). Clin Infect Dis 2015;61:324-31. https://doi.org/10.1093/cid/civ293

19. Muñoz P, Giannella M, Fanciulli C, et al. Candida tropicalis fungaemia: incidence, risk factors and mortality in a general hospital. Clin Microbiol Infect 2011;17:1538-45. https://doi.org/10.1111/j.1469-0691.2010.03338.x

20. Riddell J 4th, Kauffman CA. The evolution of resistant Candida species in cancer centers: implications for treatment and prophylaxis. Cancer 2008;112:2334-7. https://doi.org/10.1002/cncr.23465

21. Prodhan T, Yacoub AT, Jones L, et al. Non-Candida yeasts fungemia in cancer patients: a retrospective analysis at a referral cancer center, 1999-2014. Infect Dis Clin Pract 2015;23:260-2. https://doi.org/10.1097/IPC.0000000000000271