Infect Chemother. 2022 Jun;54(2):287-297
https://doi.org/10.3947/ic.2022.0024
pISSN 2093-2340·eISSN 2092-6448

Infection & Chemotherapy

Original Article

Check for updates

Clinical Implication of *Candida* Score in Multidrug-Resistant Pneumonia with Airway *Candida* Colonization

Yeonju La [1], Da Eun Kwon [2], Soyoung Jeon [3], Sujee Lee [3], Kyoung Hwa Lee [2], Sang Hoon Han [2], and Young Goo Song [2]

[1]Division of Infectious Diseases, Department of Internal Medicine, Kangwon National University Hospital, Chuncheon, Korea
[2]Division of Infectious Diseases, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[3]Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Korea

OPEN ACCESS

Received: Feb 21, 2022
Accepted: Apr 29, 2022
Published online: May 13, 2022

Corresponding Author:
Kyoung Hwa Lee, MD
Division of Infectious Diseases, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea.
Tel: +82-2-2019-4374
Fax: +82-2-3463-3882
Email: khlee0309@yuhs.ac

ORCID iDs
Yeonju La
https://orcid.org/0000-0003-2314-3699
Da Eun Kwon
https://orcid.org/0000-0003-4399-9902
Soyoung Jeon
https://orcid.org/0000-0002-9916-1917
Sujee Lee
https://orcid.org/0000-0002-2473-3693

ABSTRACT

Background: The growth of *Candida* in respiratory secretions is usually considered colonization, and antifungal therapy is rarely required. The role of *Candida* colonization in the progression of bacterial pneumonia remains controversial. The aim of this study was to identify the clinical implication of *Candida* score by analyzinge the relationship with multidrug-resistant (MDR) pneumonia and prognosis in patients with airway *Candida* colonization.
Materials and Methods: This study was a retrospective review of patients with airway *Candida* colonization by bronchial washing or bronchoalveolar lavage. The *Candida* score was calculated according to the four factors (severe sepsis, surgery at baseline, total parenteral nutrition, and multifocal *Candida* colonization). Pneumonia related mortality or hopeless discharge expecting death was defined as a poor outcome.
Results: A total of 148 patients were enrolled in the study. In a multivariate analysis model, *Candida* score was identified as an independent predictor of poor outcomes (odds ratio 2.23; 95% confidential interval 1.57 – 3.17; P <0.001) in pneumonia patients with airway *Candida* colonization. With a *Candida* score of three or higher compared with low score group, it was associated with bacterial pneumonia, especially methicillin-resistant *Staphylococcus aureus* (MRSA) infection (0.0% *vs.* 15.2%, P = 0.004). In addition, patients with a high *Candida* score had a longer hospital stay (13 *vs.* 38 days, P <0.001), longer duration of intensive care (7 *vs.* 18 days, P <0.001), and higher pneumonia-related mortality (0.0% *vs.* 45.5%, P <0.001) as compared to the low *Candida* score group. The *Candida* score showed a positive correlation with other pneumonia severity scales such as CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, and age ≥65 years) (r = 0.461, P <0.001), Pneumonia Severity Index (r = 0.397, P <0.001), and predisposition, insult, response, and organ dysfunction (PIRO) score (r = 0.425, P <0.001).
Conclusion: This study revealed that *Candida* is no longer a bystander of airway colonization, and that it affects the progression of bacterial pneumonia, including multidrug-resistant pathogens, particularly MRSA infection. Also *Candida* score can be used to predict the prognosis of patients with pneumonia.

Keywords: *Candida*; Pneumonia; Drug resistance, Microbial; Patient outcome assessment

ic Infection & Chemotherapy

Kyoung Hwa Lee
https://orcid.org/0000-0003-0033-1398
Sang Hoon Han
https://orcid.org/0000-0002-4278-5198
Young Goo Song
https://orcid.org/0000-0002-0733-4156

Funding
None.

Conflict of Interest
YGS is editorial board of Infect Chemother; however, he did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions
Conceptualization: YL, KHL. Data curation: YL, DEK. Formal analysis: KHL, SHH. Investigation: SJ, SL. Validation: SHH, YGS. Writing-original draft: YL. Writing-review & editing: KHL. Approval of final manuscript: YL, DEK, SJ, SL, KHL, SHH, YGS.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is a serious complication of mechanical ventilation (MV) with high morbidity [1, 2]. Despite intensive efforts to control known risk factors of VAP, such as semi-recumbent position, stress ulcer prophylaxis, empirical antimicrobial therapy, and early weaning attempts from ventilation, these infections are frequently accompanied by high mortality rates, long-term hospitalization, and increased medical costs [3]. As most causes of VAP are bacterial species, the role of fungal pathogens in immune-competent hosts is unclear [4]. Isolation of *Candida* species in bronchial washing or lavage samples is not unusual for patients in the intensive care unit. *Candida* is found in approximately 30% of patients with MV care for more than 48 hours and is found in more than 40% of critically ill patients with MV care [5], although progression to *Candida*-associated fungal pneumonia is rare [6, 7]. Thus, the growth of *Candida* in respiratory secretions is usually considered colonization, and antifungal therapy is rarely required. Some data show that there is no clinical correlation between VAP and airway colonization with *Candida* species, suggesting that *Candida* colonization does not affect the progression of bacterial pneumonia [8, 9].

However, according to recent studies, *Candida* may no longer be considered a bystander in the airways [10]. *Candida* colony formation affects bacterial pneumonia, and there are reports that it is particularly associated with VAP caused by multi-drug resistant (MDR) *Pseudomonas aeruginosa* or *Acinetobacter baumannii* [11-13]. In a rat model with *Candida albicans* airway colonization, researchers observed the promotion of bacterial pneumonia, via elicited helper T cell immune responses and then inhibition of bacterial phagocytosis by alveolar macrophages [14].

When *Candida* infection is suspected, fungal cultures for diagnosis take considerable time, and clinicians struggle to decide about when to start the administration of antifungal agents to prevent or treat fungal infections. As mortality increases when prompt treatment is delayed, clinical prediction models have been developed. These prediction tools include the *Candida* colonization index and *Candida* score [15], which have been used to predict the prognosis of *Candida* infection in patients with *Candida* colonization.

We aimed to analyze whether these scales can help predict the progress of bacterial pneumonia, especially pneumonia associated with MDR pathogens. Therefore, the clinical implication of *Candida* score was identified by analyzinge the relationship with MDR pneumonia and prognosis in patients with airway *Candida* colonization.

MATERIALS AND METHODS

1. Study design and population

This study is a retrospective review of patients with airway *Candida* colonization at the Gangnam Severance Hospital, a tertiary center in Seoul, Korea, from January 2007 to April 2020. During this period, clinical data from the patients with *Candida* species isolated by bronchial washing or bronchoalveolar lavage were obtained. Patients with invasive candidiasis such as candidemia or esophageal candidiasis were excluded from this study.

2. Ethics statement

The protocol for this retrospective study was reviewed and approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine in Seoul,

https://doi.org/10.3947/ic.2022.0024

Republic of Korea (Reg. No. 3-2020-0482). The board waived the requirement for informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki.

3. Clinical variables and definition

Clinical information was reviewed retrospectively for demographic features, including age, sex, and comorbidities. The definition of pneumonia was determined according to the American Thoracic Society/Infectious Diseases Society of America guidelines. Three types of pneumonia were stratified, community-acquired pneumonia (CAP) is defined as pneumonia that develops in the community. In turn, hospital-acquired pneumonia (HAP) is pneumonia that occurs 48 hours or more after admission in a hospital setting and is not incubating at the time of hospital admission. The VAP is defined as pneumonia after 48 hours of endotracheal intubation and ventilator care [16, 17]. The distinction between favorable and poor outcome was determined according to the patients' condition at the time of hospital discharge. If the patient died or was transferred to a long-term care facility and the prognosis was expected to death, the outcome was classified as poor outcome.

The *Candida* score and index were assessed based on the initial *Candida* isolation status. Colonization was defined as the presence of *Candida* species in non-sterile body parts or body fluids [18]. Bronchoscopy was performed in the early stages of pneumonia, and bronchoalveolar lavage and washing culture were carried out at the same time. Patients with airway *Candida* colonization were those with *Candida* species incubated in the respiratory tract determined via bronchoscopy, including bronchoalveolar lavage or bronchial washing culture. The *Candida* score was calculated cross-sectionally based on the time point at which bronchoscopy was conducted. The *Candida* colonization index is defined as the ratio of the number of *Candida* species cultured in body sites other than blood to the total number of cultured body sites [19]. The *Candida* score was calculated according to the presence of four components (range, 0 - 5 points): severe sepsis (2 points), surgery at baseline (1 point), total parenteral nutrition (TPN) (1 point), and multifocal *Candida* colonization (1 point). In the other previous studies, if the cutoff score was three or higher, there was a high risk of developing candidiasis, with a sensitivity of 61.0% and a specificity of 86.0%. Therefore, we divided patients into two groups, a high-grade *Candida* score group with a range of three to five points and a low-grade *Candida* score group with a range of zero through two points [15, 20].

Pneumonia severity scales such as CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, and age ≥65 years) [21], Pneumonia Severity Index (PSI) [22], and predisposition, insult, response, and organ dysfunction (PIRO) score [23-25] were also calculated concurrently when assessing *Candida* score. The components of PSI were sex, cormobidities, vital signs, mental status, arterial blood gas analysis, and so on. The parameters of the PIRO score are predisposition (chronic illness, age, comorbidities), insult (injury, bacteremia, endotoxin), response (neutropenia, hypoxemia, hypotension), and organ dysfunction. Other clinical data- causative pathogen of pneumonia, antimicrobial susceptibility test, use of antifungal agent for *Candida* species, duration of hospitalization, and duration of intensive care unit (ICU) care were extracted.

Categories of Gram-positive and Gram-negative strains were determined by Gram staining. Antimicrobial susceptibility tests were confirmed according to the breakpoint of Clinical and Laboratory Standards Institute-guidelines [26]. We identified whether carbapenemase-producing *Enterobacteriaceae* (CPE), MDR *A. baumannii* (MRAB), MDR *P. aeruginosa* (MRPA), and methicillin-resistant *Staphylococcus aureus* (MRSA) were isolated from airway specimens. The

https://doi.org/10.3947/ic.2022.0024

identified strains were bacterial pathogens clinically considered to be the causative pathogen of pneumonia, and only strains grown in class IV (10 - 25 epithelial cells and >25 leukocytes per field) or V (≤10 epithelial cells and >25 leukocytes per field) of the Murray-Washington grouping system, and bronchoalveolar lavage or bronchial washing culture were included.

The data of using anti fungal agents were extracted, and since invasive candidiasis was excluded in this study, the use of antifungal agents was not used as definite therapy for fungal diseases. The criteria for use of antifungal drugs depended on the judgment of physicians, considering the patient's medical history and rapid deterioration during treatment. These conditions include neutropenia, long-term ventilator treatment, and *Candida* growth at multiple sites, while high-risk patients in the ICU setting used fluconazole to prevent invasive candidiasis [18, 27]. All data were collected until death or patient discharge.

4. Statistical analysis

Categorical variables were compared using the Chi-square test or Fisher's exact test and expressed as number (percent). Continuous variables were expressed as median with interquartile range (IQR). Continuous variables between two groups were compared using the non-parametric Mann–Whitney *U* test. Significant clinical variables in primary analysis (*P*-value ≤0.05) were reviewed by multivariate logistic regression. Clinical correlation among other scales such as CURB-65, PSI, PIRO and *Candida* score was evaluated by spearman correlation analysis. All two-tailed *P*-values or adjusted *P*-values of ≤0.05 were considered statistically significant. All statistical analyses were performed using SPSS V23 software (IBM Corp., Armonk, NY, USA).

RESULTS

1. Candida species distribution in patients with airway *Candida* colonization

From January 2007 to April 2020, clinical data from 176 patients with *Candida* species isolated by bronchial washing or bronchoalveolar lavage were retrieved. Among them, only 163 patients were adults, six patients were excluded due to invasive candidiasis with candidemia, and nine patients were excluded because of insufficient clinical data. Finally, a total of 148 patients with *Candida* colonization in the respiratory tract confirmed by bronchoscopy were included in this study (**Fig. 1**).

Of the 148 pneumonia patients who showed *Candida* colonies in the results of bronchoscopy, 91 patients eventually had favorable progression and 57 colonizers progressed to poor results. According to the distribution of *Candida* species, *C. albicans* was the predominant species (64.8% in the favorable outcome group and 57.9% in the poor outcome group), and *C. tropicalis* (14.3% and 14.0%, respectively) was the second most common pathogen, followed by *C. glabrata* (3.3% and 3.5%, respectively), in airway colonization between the two groups (**Fig. 2**).

2. Predictive factor of poor outcome in patients with airway *Candida* colonization

Comorbidity with hypertension (42.9% *vs.* 63.2%, $P = 0.016$), diabetes (26.4% *vs.* 42.1%, $P = 0.047$), and autoimmune disease (3.3% *vs.* 14.0%, $P = 0.023$) were significant risk factors for poor prognosis as compared to favorable prognosis. Immunocompromised factors such as end-stage renal disease with regular hemodialysis, lung cancer, and use of steroids (prednisolone ≥20 mg/day more than 2 weeks) did not affect the disease outcome of the

https://doi.org/10.3947/ic.2022.0024

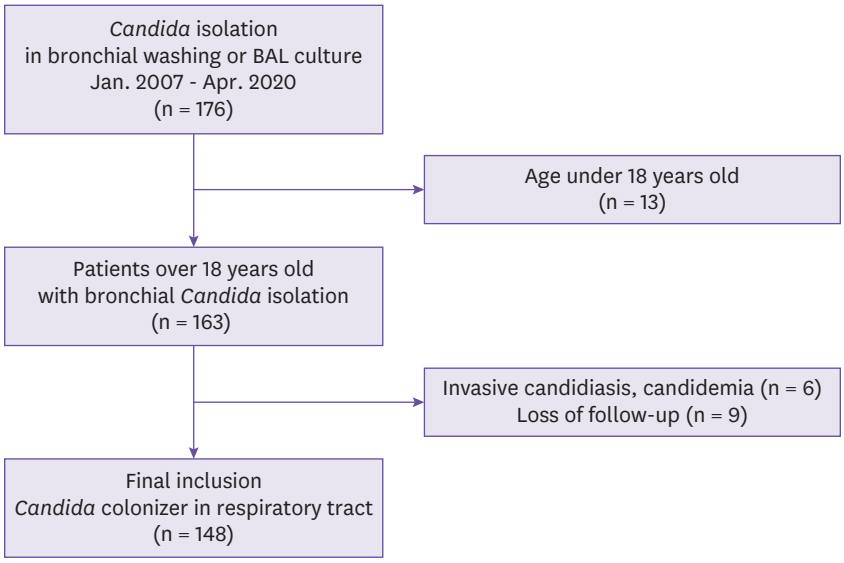

Figure 1. Flow chart of study population.
BAL, broncho-alveolar lavage.

airway *Candida* colonizer. There were no cases of solid organ transplant or hematopoietic stem cell transplant recipients among the subjects in this study. The median *Candida* score was higher in the poor outcome group than in the favorable outcome group (2.0 *vs.* 4.0 days, respectively, P <0.001), while the median *Candida* index showed no specific differences between the two groups (**Table 1**). Anaysis in each respective factor of *Candida* score, sepsis (48.3% *vs.* 96.5%, P <0.001) and TPN (50.5% *vs.* 100.0%, P <0.001) showed significant differences between favorable and poor groups. Other prognostic scales for pneumonia, CURB-65 (1.0 *vs.* 2.0 points, P <0.001), PSI (110.0 *vs.* 136.0 points, P <0.001), and PIRO (2.0 *vs.* 4.0 points, P <0.001), also demonstrated similar trend. The clinical variables that were significant in the primary analysis were reviewed in the multivariate analysis (**Table 2**). CURB-65, PSI or PIRO score were also significant variables, but they are excluded in multivariate analysis due to the multicollinearity. Finally, the *Candida* score was identified as an independent predictor of poor outcomes (odds ratio [OR], 2.23; 95% confidential Interval [CI], 1.57–3.17; P <0.001).

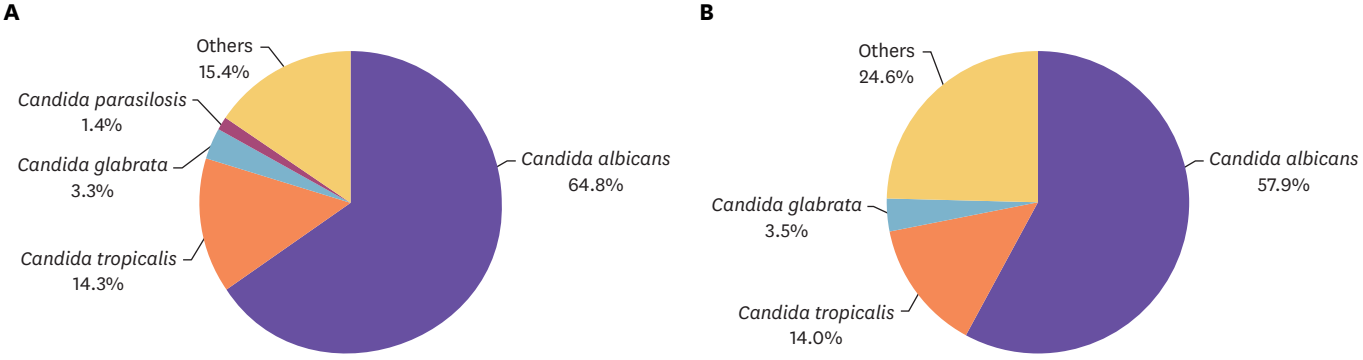

Figure 2. Distribution of *Candida* species isolated from bronchial washing and bronchoalveolar lavage. (A) Favorable outcome group, (B) Poor outcome group.

https://doi.org/10.3947/ic.2022.0024

Table 1. Baseline characteristics of pneumonia patients with airway *Candida* colonization

Variables	Favorable outcome (n = 91)	Poor outcome (n = 57)	*P*-value
Age, years	70.0 [60.0 - 78.0]	74.0 [65.0 - 82.0]	0.098[b]
Sex, male	66 (72.5)	40 (70.2)	0.757[c]
Comorbidity			
Hypertension	39 (42.9)	36 (63.2)	0.016[c]
Diabetes	24 (26.4)	24 (42.1)	0.047[c]
Pulmonary tuberculosis	17 (18.7)	12 (21.1)	0.724[c]
Hepatitis	1 (1.1)	2 (3.5)	0.559[d]
CVA	10 (11.0)	2 (3.5)	0.130[d]
ESRD on HD	9 (9.9)	3 (5.3)	0.372[d]
COPD	5 (5.5)	6 (10.5)	0.337[d]
Lung cancer	8 (8.8)	11 (19.3)	0.063[c]
ILD	2 (2.2)	5 (8.8)	0.108[d]
Autoimmune disease	3 (3.3)	8 (14.0)	0.023[d]
Steroid use[a]	12 (13.2)	6 (10.5)	0.630[c]
Candida score, points	2.0 [1.0 - 4.0]	4.0 [3.0 - 4.0]	<0.001[b]
Sepsis, n (%)	44 (48.3)	55 (96.5)	<0.001[c]
TPN, n (%)	46 (50.5)	57 (100)	<0.001[c]
Surgery at baseline, n (%)	12 (13.1)	6 (10.5)	0.629[c]
Multifocal *Candida* colonization, n (%)	59 (64.8)	42 (73.7)	0.260[c]
Candida index	0.5 [0.3 - 0.5]	0.5 [0.5 - 0.5]	0.115[b]
CURB-65, points	1.0 [1.0 - 2.0]	2.0 [2.0 - 3.0]	<0.001[b]
Pneumonia Severity Index, points	110.0 [88.0 - 133.0]	136.0 [108.5 - 164.5]	<0.001[b]
Pneumonia Severity Index, category			<0.001[d]
I (<50 points)	2 (2.2)	0 (0)	
II (51 - 70 points)	10 (11.0)	0 (0)	
III (71 - 90 points)	12 (13.1)	4 (7.0)	
IV (91 - 130 points)	43 (47.3)	17 (29.8)	
V (131 - 395 points)	24 (26.4)	36 (63.2)	
PIRO score, points	2.0 [2.0 - 4.0]	4.0 [3.0 - 5.0]	<0.001[b]

Data are expressed by number (%) and median [25% - 75% IQR].
[a]Use of prednisolone ≥ 20 mg/day more than 2 weeks.
[b]Mann-Whitney *U* test.
[c]Pearson's chi-squared test.
[d]Fisher's exact test.
COPD, chronic obstructive pulmonary disease; CURB-65, confusion, urea, respiratory rate, blood pressure, age ≥65 years; CVA, cerebrovascular accident; ESRD, end-stage renal disease; HD, hemodialysis; ILD, interstitial lung disease; PIRO, predisposition, insult, response, and organ dysfunction; TPN, total parenteral nutrition.

Table 2. Prognostic factors for poor outcomes among pneumonia patients with airway *Candida* colonization using multivariate logistic regression

Variables	OR	95% CI	*P*-value
Hypertension	1.26	0.57 - 2.79	0.577
Diabetes	1.39	0.62 - 3.10	0.425
Autoimmune diseases	2.45	0.59 - 10.13	0.217
Candida score	2.23	1.57 - 3.17	<0.001

OR, odds ratio; CI, confidence interval.

3. Clinical implication of *Candida* score with cut-off value above three points

When the *Candida* score was divided into two different levels (high grade, 3 - 5 points; and low grade, 0 - 2 points), high *Candida* scores ≥3 was significantly correlated with bacterial identification (32.7% in the low *Candida* score group *vs.* 65.7% in the high *Candida* score group, P <0.001), especially with MDR pathogens (14.3% *vs.* 39.4%, P = 0.002) compared with low *Candida* scores. There were no clinical differences in age, sex, and types of pneumonia, such as CAP, HAP, and VAP, between the two groups. Among isolated MDR bacterial pathogens, MDR Gram-positive cocci were significantly dominant in the group with a high *Candida* score (0.0% *vs.* 17.2%, P = 0.002) as compared to the low *Candida* score group. In particular, MRSA

https://doi.org/10.3947/ic.2022.0024

Table 3. Clinical implication of *Candida* score among pneumonia patients with airway *Candida* colonization

Variables	Low CS ≤2 (n = 49)	High CS ≥3 (n = 99)	*P*-value
Age, years	70.0 [63.5 - 79.5]	72.0 [62.0 - 80.0]	0.721[b]
Sex, male	15 (30.6)	27 (27.3)	0.672[c]
Type of pneumonia			0.145[c]
CAP	32 (65.3)	55 (55.6)	
HAP	16 (32.7)	33 (33.3)	
VAP	1 (2.0)	11 (11.1)	
Isolated bacteria[a], n (%)	16 (32.7)	65 (65.7)	<0.001[c]
Isolated MDR bacteria, n (%)	7 (14.3)	39 (39.4)	0.002[c]
MDR-Gram negative rods	7 (14.3)	24 (24.2)	0.161[c]
MDR-Gram positive cocci	0 (0)	17 (17.2)	0.002[c]
CPE	3 (6.1)	5 (5.1)	>0.786[c]
MRAB	3 (6.1)	13 (13.1)	0.196[c]
MRPA	1 (2.0)	6 (6.1)	0.426[d]
MRSA	0 (0)	15 (15.2)	0.004[d]
Use of fluconazole, n (%)	7 (14.3)	34 (34.3)	0.010[c]
All cause of mortality, n (%)	6 (12.2)	46 (48.4)	<0.001[c]
Pneumonia-related mortality, n (%)	0 (0.0)	45 (45.5)	<0.001[c]
Duration, days, n (%)			
Hospital stay	13.0 (9.3 - 28.0)	38.0 (18.5 - 53.0)	<0.001[b]
ICU stay	7.0 (0.8 - 8.3)	18.0 (10.3 - 36.8)	<0.001[b]
From admission until airway *Candida* colonization	6.0 (3.3 - 9.8)	7.5 (3.0 - 16.0)	<0.001[b]
From mechanical ventilation until airway *Candida* colonization	2.5 (−4.8 - 7.5)	2.0 (0 - 6.8)	0.921[b]

Data are expressed by number (%) and median [25% - 75% IQR].
[a]Isolated bacteria within the respiratory tract.
[b]Mann-Whitney *U* test.
[c]Pearson's chi-squared test.
[d]Fisher's exact test.
CS, *Candida* score; CAP, community-acquired pneumonia; CPE, carbapenemase-producing *Enterobacteriaceae*; HAP, hospital-acquired pneumonia; MDR, multidrug-resistant; MRAB, multidrug-resistant *Acinetobacter baumannii*; MRPA, multidrug-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

was the dominant pathogen in the high *Candida* score group as compared to the low *Candida* score group (0.0% *vs.* 15.2%, $P = 0.004$), whereas MDR Gram-negative rods, including CPE, MRAB, and MRPA, showed no significant differences between the two groups.

Despite frequent use of antifungal agents such as fluconazole in the high *Candida* score group (14.3% *vs.* 34.3%, $P = 0.010$), the median length of hospitalization (13 *vs.* 38 days, $P < 0.001$), duration of ICU stay (7 *vs.* 18 days, $P < 0.001$), all-cause mortality (12.2% *vs.* 48.4%, $P < 0.001$), pneumonia-related mortality (0.0% *vs.* 45.5%, $P < 0.001$), and duration from admission until airway *Candida* colonization (6.0 *vs.* 7.5 days, $P < 0.001$) were significantly higher in the high *Candida* score group than the low *Candida* score group (**Table 3**). The *Candida* score showed a positive correlation with other pneumonia severity scales such as CURB-65 ($r = 0.461$, 95% CI [0.333 - 0.582], $P < 0.001$), PSI ($r = 0.397$ [0.251 - 0.525], $P < 0.001$), and PIRO score ($r = 0.425$ [0.289 - 0.553], $P < 0.001$) (**Table 4**).

Table 4. Correlation analysis using spearman model between the pneumonia severity scale and *Candida* score

Variables	*Candida* score *r* (95% CI)	*P*-value
CURB-65	0.461 (0.333 – 0.582)	<0.001
Pneumonia severity index	0.397 (0.251 – 0.525)	<0.001
PIRO score	0.425 (0.289 – 0.553)	<0.001

CI, Confidence interval; CURB-65, confusion, urea, respiratory rate, blood pressure, age ≥65 years; PIRO, predisposition, insult, response, and organ dysfunction.

https://doi.org/10.3947/ic.2022.0024

ic Infection & Chemotherapy

DISCUSSION

In this study, we found that underlying comorbidities such as hypertension, diabetes, autoimmune disease, and high mean *Candida* score could be a risk factor for poor outcomes in patients with bacterial pneumonia and airway *Candida* colonization. In particular, the *Candida* score was an independent predictor of disease progression, with an OR of 2.23 in multivariate logistic regression. Previous studies have reported an increased risk of poor prognosis or invasive candidiasis in patients with a *Candida* score of three or higher [15, 20], and it has been demonstrated that airway *Candida* colonization affects mortality and disease severity in immunocompromised patients [28]. However, in these data, end-stage renal diseases, lung cancer, and steroid therapy did not clearly impact the disease course. There were no cases of obvious immunocompromised patients such as solid organ transplant or hematopoietic stem cell transplant recipients. Therefore, the impact may be more severe in these population, and further analysis of this subgroup is needed. As already demonstrated in other studies, there was no effect of antifungal prophylaxis on disease outcome regardless of *Candida* score [9, 27].

The proportion of bacteria thought to be the causative pathogen of pneumonia was also predominant in the high *Candida* score group and mostly included MDR pathogens (MRSA, CPE, MRPA, and MRAB). In particular, MRSA was found to be significantly dominant. Although controversial, *Candida*-colonized pneumonia is known to be associated with VAP, especially MRPA or MRAB. Previous studies showed that *Candida* colonization is mostly associated with Gram-negative pathogen identification. These studies showed that *Candida* colonization is no longer a bystander, and that it increases bacterial virulence and decreases bacterial clearance [29]. In our analysis, the proportion of causative bacteria of MRPA or MRAB was high but was not significant. Rather, it was interesting to note that it mostly included MRSA.

The actual mechanism of how *Candida* colonies lead to more serious consequences of bacterial pneumonia remains unclear. Several previous *in vitro* or *in vivo* studies have confirmed the interaction between *Candida* and bacteria. Mixed bacterial–fungal colonies are common in patients with pneumonia, especially those who have received ventilator care, forming a mixed biofilm. These colonies interact directly or indirectly and affect each other's survival or virulence. Physical interactions can attach bacteria to the surface of fungal hyphae, change the pH of the environment, and create metabolites or chemicals for polymicrobial coexistence [29, 30]. Microscopy and immunoassay demonstrated that *S. aureus* binds to fungal biofilm, and in this process, agglutin-like sequence 3 (Als3p) of *C. albicans* plays a key role in adherence to *S. aureus* [31]. In a mouse model study, *C. albicans* enhanced the virulence of *S. aureus* strains. A minimum dose of *C. albicans* between 1.1×10^5 and 1.1×10^7 colony-forming units was necessary for the amplification for virulence of *S. aureus* [32].

Biofilms inhibit the penetration rate of antibiotic agents and reduce the efficacy of antibiotics. *S. aureus* can be coated with *Candida* matrix within the polymicrobial biofilm, and *S. aureus* resistance to vancomycin was increased after being coated with the isolated *Candida* matrix [33, 34].

And when CURB-65, pneumonia severity index, and PIRO score were analyzed as variables, there was a significant difference according to the prognosis of pneumonia. In addition, a comparative analysis of the correlation between various pneumonia severity scales and *Candida* score was performed as shown in **Table 4**, it was confirmed that the *Candida* score had a positive correlation with them, so that it can be used to predict the prognosis of pneumonia

https://doi.org/10.3947/ic.2022.0024

patients. Analysis by component of *Candida* score showed that sepsis and TPN use were significant, suggesting that these major factors may effect poor prognosis.

This study has several limitations. First, this research was a retrospective review that relied on electronic medical records and was conducted in a single center. It is believed that biofilm formation leads to lower antibiotic penetration, causing to an increase antimicrobial resistance. Therefore, further prospective studies using clinical samples should be conducted to validate our hypothesis.Second, the exclusion of invasive candidiasis was not confirmed by histopathology. There were no cases of serious invasive candidiasis requiring lung biopsy, and there was no evidence of invasive fungal infection on chest computed tomography scan images. Patients with bacterial pneumonia and candidemia were excluded from the study. Lastly, MRSA is also a strain that can be colonized in VAP patients, and further analysis should be performed on more large scale subjects with airway *Candida* colonization comparing with control group. The point of this study is to predict infection with the MDR pathogen based on *Candida* and provide clinical evidence for preemptive response through early intervention. In addition, it does not raise the risk of all MDR pathogens, and in the case of MDR-Gram negative rods, the *P*-value was insignificant, and MRSA showed especially dominant findings. This results are thought to be a clinical verification of experimental data that has demonstrated interactions between *Candida* with MRSA in many previous studies.

In conclusion, the *Candida* score may be a predictive prognostic factor in patients with pneumonia and airway *Candida* colonization. A *Candida* score of three or higher can be a risk factor for poor outcomes due to longer hospitalization, prolonged ICU stays, and high mortality associated with pneumonia. The clinical implicaion of a high *Candida* score is associated with bacterial pathogens of pneumonia, especially MRSA. This study revealed that *Candida* is no longer a bystander of airway colonization, and that it affects the progression of bacterial pneumonia, including that caused by MDR pathogens.

ACKNOWLEDGEMENTS

We thank the colleagues of Biostatistics Collaboration Unit in Gangnam Severance Hospital for their expert help and assistance.

REFERENCES

1. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867-903.
PUBMED | CROSSREF
2. Markowicz P, Wolff M, Djedaïni K, Cohen Y, Chastre J, Delclaux C, Merrer J, Herman B, Veber B, Fontaine A, Dreyfuss D; ARDS Study Group. Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. Am J Respir Crit Care Med 2000;161:1942-8.
PUBMED | CROSSREF
3. Bouadma L, Deslandes E, Lolom I, Le Corre B, Mourvillier B, Regnier B, Porcher R, Wolff M, Lucet JC. Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit. Clin Infect Dis 2010;51:1115-22.
PUBMED | CROSSREF
4. Delisle MS, Williamson DR, Albert M, Perreault MM, Jiang X, Day AG, Heyland DK. Impact of *Candida* species on clinical outcomes in patients with suspected ventilator-associated pneumonia. Can Respir J 2011;18:131-6.
PUBMED | CROSSREF

5. Knox KS, Meinke L. Role of bronchoalveolar lavage diagnostics in fungal infections. Clin Chest Med 2009;30:355-65, viii.
PUBMED | CROSSREF
6. el-Ebiary M, Torres A, Fàbregas N, de la Bellacasa JP, González J, Ramirez J, del Baño D, Hernández C, Jiménez de Anta MT. Significance of the isolation of *Candida* species from respiratory samples in critically ill, non-neutropenic patients. An immediate postmortem histologic study. Am J Respir Crit Care Med 1997;156:583-90.
PUBMED | CROSSREF
7. Meersseman W, Lagrou K, Spriet I, Maertens J, Verbeken E, Peetermans WE, Van Wijngaerden E. Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study. Intensive Care Med 2009;35:1526-31.
PUBMED | CROSSREF
8. Timsit JF, Schwebel C, Styfalova L, Cornet M, Poirier P, Forrestier C, Ruckly S, Jacob MC, Souweine B. Impact of bronchial colonization with *Candida* spp. on the risk of bacterial ventilator-associated pneumonia in the ICU: the FUNGIBACT prospective cohort study. Intensive Care Med 2019;45:834-43.
PUBMED | CROSSREF
9. Terraneo S, Ferrer M, Martín-Loeches I, Esperatti M, Di Pasquale M, Giunta V, Rinaudo M, de Rosa F, Li Bassi G, Centanni S, Torres A. Impact of *Candida* spp. isolation in the respiratory tract in patients with intensive care unit-acquired pneumonia. Clin Microbiol Infect 2016;22:94.e1-8.
PUBMED | CROSSREF
10. Ricard JD, Roux D. *Candida* colonization in ventilated ICU patients: no longer a bystander! Intensive Care Med 2012;38:1243-5.
PUBMED | CROSSREF
11. Hamet M, Pavon A, Dalle F, Pechinot A, Prin S, Quenot JP, Charles PE. *Candida* spp. airway colonization could promote antibiotic-resistant bacteria selection in patients with suspected ventilator-associated pneumonia. Intensive Care Med 2012;38:1272-9.
PUBMED | CROSSREF
12. Azoulay E, Timsit JF, Tafflet M, de Lassence A, Darmon M, Zahar JR, Adrie C, Garrouste-Orgeas M, Cohen Y, Mourvillier B, Schlemmer B; Outcomerea Study Group. *Candida* colonization of the respiratory tract and subsequent pseudomonas ventilator-associated pneumonia. Chest 2006;129:110-7.
PUBMED | CROSSREF
13. Tan X, Zhu S, Yan D, Chen W, Chen R, Zou J, Yan J, Zhang X, Farmakiotis D, Mylonakis E. *Candida* spp. airway colonization: a potential risk factor for *Acinetobacter baumannii* ventilator-associated pneumonia. Med Mycol 2016;54:557-66.
PUBMED | CROSSREF
14. Roux D, Gaudry S, Khoy-Ear L, Aloulou M, Phillips-Houlbracq M, Bex J, Skurnik D, Denamur E, Monteiro RC, Dreyfuss D, Ricard JD. Airway fungal colonization compromises the immune system allowing bacterial pneumonia to prevail. Crit Care Med 2013;41:e191-9.
PUBMED | CROSSREF
15. León C, Ruiz-Santana S, Saavedra P, Galván B, Blanco A, Castro C, Balasini C, Utande-Vázquez A, González de Molina FJ, Blasco-Navalproto MA, López MJ, Charles PE, Martín E, Hernández-Viera MA; Cava Study Group. 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;37:1624-33.
PUBMED | CROSSREF
16. Corrado RE, Lee D, Lucero DE, Varma JK, Vora NM. Burden of adult community-acquired, health-care-associated, hospital-acquired, and ventilator-associated pneumonia: New York City, 2010 to 2014. Chest 2017;152:930-42.
PUBMED | CROSSREF
17. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM Jr, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:e61-111.
PUBMED | CROSSREF
18. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1-50.
PUBMED | CROSSREF
19. Eggimann P, Pittet D. *Candida* colonization index and subsequent infection in critically ill surgical patients: 20 years later. Intensive Care Med 2014;40:1429-48.
PUBMED | CROSSREF

20. Leroy G, Lambiotte F, Thévenin D, Lemaire C, Parmentier E, Devos P, Leroy O. Evaluation of "*Candida* score" in critically ill patients: a prospective, multicenter, observational, cohort study. Ann Intensive Care 2011;1:50.
PUBMED | CROSSREF
21. Jones BE, Jones J, Bewick T, Lim WS, Aronsky D, Brown SM, Boersma WG, van der Eerden MM, Dean NC. CURB-65 pneumonia severity assessment adapted for electronic decision support. Chest 2011;140:156-63.
PUBMED | CROSSREF
22. Aujesky D, Fine MJ. The pneumonia severity index: a decade after the initial derivation and validation. Clin Infect Dis 2008;47(Suppl 3):S133-9.
PUBMED | CROSSREF
23. Rello J, Rodriguez A, Lisboa T, Gallego M, Lujan M, Wunderink R. PIRO score for community-acquired pneumonia: a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. Crit Care Med 2009;37:456-62.
PUBMED | CROSSREF
24. Rello J. Demographics, guidelines, and clinical experience in severe community-acquired pneumonia. Crit Care 2008;12(Suppl 6):S2.
PUBMED | CROSSREF
25. Lisboa T, Diaz E, Sa-Borges M, Socias A, Sole-Violan J, Rodríguez A, Rello J. The ventilator-associated pneumonia PIRO score: a tool for predicting ICU mortality and health-care resources use in ventilator-associated pneumonia. Chest 2008;134:1208-16.
PUBMED | CROSSREF
26. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing. 31st ed. CLSI supplement M100. CLSI; 2021.
27. Lindau S, Nadermann M, Ackermann H, Bingold TM, Stephan C, Kempf VA, Herzberger P, Beiras-Fernandez A, Zacharowski K, Meybohm P. Antifungal therapy in patients with pulmonary *Candida* spp. colonization may have no beneficial effects. J Intensive Care 2015;3:31.
PUBMED | CROSSREF
28. Pendleton KM, Dickson RP, Newton DW, Hoffman TC, Yanik GA, Huffnagle GB. Respiratory tract colonization by *Candida* species portends worse outcomes in immunocompromised patients. Clin Pulm Med 2018;25:197-201.
PUBMED | CROSSREF
29. Peleg AY, Hogan DA, Mylonakis E. Medically important bacterial-fungal interactions. Nat Rev Microbiol 2010;8:340-9.
PUBMED | CROSSREF
30. Frey-Klett P, Burlinson P, Deveau A, Barret M, Tarkka M, Sarniguet A. Bacterial-fungal interactions: hyphens between agricultural, clinical, environmental, and food microbiologists. Microbiol Mol Biol Rev 2011;75:583-609.
PUBMED | CROSSREF
31. Peters BM, Ovchinnikova ES, Krom BP, Schlecht LM, Zhou H, Hoyer LL, Busscher HJ, van der Mei HC, Jabra-Rizk MA, Shirtliff ME. *Staphylococcus aureus* adherence to Candida albicans hyphae is mediated by the hyphal adhesin Als3p. Microbiology (Reading) 2012;158:2975-86.
PUBMED | CROSSREF
32. Carlson E. Enhancement by Candida albicans of *Staphylococcus aureus, Serratia marcescens*, and *Streptococcus faecalis* in the establishment of infection in mice. Infect Immun 1983;39:193-7.
PUBMED | CROSSREF
33. Harriott MM, Noverr MC. *Candida albicans* and *Staphylococcus aureus* form polymicrobial biofilms: effects on antimicrobial resistance. Antimicrob Agents Chemother 2009;53:3914-22.
PUBMED | CROSSREF
34. Harriott MM, Noverr MC. Ability of *Candida albicans* mutants to induce *Staphylococcus aureus* vancomycin resistance during polymicrobial biofilm formation. Antimicrob Agents Chemother 2010;54:3746-55.
PUBMED | CROSSREF