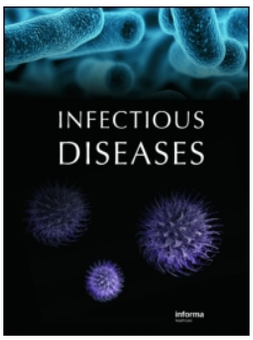

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ORIGINAL ARTICLE

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Risk factors of septic shock development and thirty-day mortality with a predictive model in adult candidemia patients in intensive care units

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ABSTRACT

Background: This study aimed to investigate factors associated with septic shock development and 30-day mortality outcome with a prediction model among adult candidemia patients in the intensive care unit (ICU).

Methods: A retrospective study was conducted among patients admitted to the ICU from 2009 to 2018 at a tertiary care medical centre. The study subjects included adult patients $\geq$ 19 years with candidemia treated with antifungal agent for $\geq$ 3 days. Clinical variables were collected and analysed.

Results: A total of 126 patients were included in the study. Of these patients, 32 patients (25.4%) had septic shock. Multivariate logistic regression analysis revealed that chronic liver disease was associated with septic shock (odds ratio [OR] 3.372, 95% confidence interval [CI] 1.057 – 10.057). The rate of 30-day mortality was 35.7% and the associated mortality risk factors were malignancy (OR 8.251, 95% CI 2.227 – 30.573), chronic liver disease (OR 3.605, 95% CI 0.913 – 14.227), haemodialysis (OR 8.479, 95% CI 1.801 – 39.924), mycological failure (OR 29.675, 95% CI 7.012 – 125.578), and septic shock (OR 3.980, 95% CI 1.238 – 12.796). A predictive model for 30-day mortality was created based on the mortality risk factor scores, which had an area of 0.862 under the receiver operating characteristic curve.

Conclusions: Adult candidemia patients in the ICU who have chronic liver disease may be at higher risk of developing septic shock. Furthermore, our predictive model for 30-day mortality based on the mortality risk factors may be useful for clinical assessment.

Abbreviations: ICU: Intensive care unit; ROK: Republic of Korea; EORTC/MSG: European Organisation for the Research and Treatment of Cancer/Mycoses Study Group; IQR: inter-quartile ranges; ROC: receiver operating characteristic curve; AUC: area under the curve; CVC: central venous catheter

KEYWORDS
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Supplemental data for this article can be accessed here.

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Background

Candidemia is globally recognized as one of the leading causes of nosocomial bloodstream infections in the intensive care unit (ICU) with significant morbidity and mortality [1–3]. Previous studies reported that the mortality rate of candidemia was known to be around 30% [4,5]. Septic shock is also one of the leading causes of death in patients in the ICU. Septic shock may account for 10% of ICU admission, and septic shock-related mortality has ranged from 20% to 40% [6,7]. Although septic shock due to bacterial infection has been well studied [8] with the recent improvement of the mortality rate [9,10], there has been a paucity of data regarding candidemia-related septic shock due to its relatively infrequent occurrence [11]. Despite the limited availability of clinical data, previous studies have found several risk factors of septic shock among candidemia patients such as old age, comorbidities, haemodialysis, and admission to the ICU [12–16]. Also, predictive models for mortality have been investigated among candidemia patients [17,18]. However, risk factors of septic shock and the predictive mortality model among candidemia patients in the ICU have not been well defined and might vary depending on the clinical setting. Therefore, our study aimed to investigate factors associated with septic shock development and 30-day mortality outcome with the prediction model among adult candidemia patients in the ICU.

Methods

Study design and patients

A retrospective study was conducted among patients admitted to the ICU from 2009 to 2018 at a tertiary care medical centre, Seoul, Republic of Korea (ROK). Inclusion criteria were (1) adult patients $\geq$ 19 years admitted to the ICU, (2) patients diagnosed with candidemia, and (3) receipt of systemic antifungal treatment $\geq$ 3 days. If a patient had more than one episode of candidemia, only the first episode of candidemia was considered. Exclusion criteria were (1) patients $<$19 years, (2) patients treated with systemic antifungal therapy $<$3 days, and (3) patients with concomitant bacteraemia. The study protocol was approved by the institutional review board of Korea University Anam Hospital (IRB Number 2018AN0440). As this was an observational study, informed consent was not required.

Clinical data and definitions

Demographics and clinical data including comorbidities, clinical conditions such as mechanical ventilation, urinary catheterization, central venous catheterization, receipt of recent surgery, use of steroid, total parenteral nutrition, haemodialysis, chemotherapy, presence of neutropenia, previous admission to ICUs within 3 months, previous use of antibiotics within 1 month, *Candida* species of candidemia, sources of candidemia, and treatment outcomes, were collected after reviewing the electronic medical records. The Charlson comorbidity index was calculated to evaluate the impact of underlying comorbidities. The presence of neutropenia was defined as an absolute neutrophil count of $<$500 cells/mm^3. The use of systemic steroid was defined as $\geq$20 mg/day of prednisone equivalent. Candidemia was defined as at least one positive peripheral blood culture for *Candida* species obtained from patients. Identification of *Candida* species from blood culture was determined using BacT/ALERT® 3D Microbial Detection System (bioMérieux, Inc., Durham, NC, USA). Antifungal susceptibility of *Candida* species was performed using the automated Vitek® 2 Yeast Biochemical Card (bioMérieux, Inc.). The definition of septic shock was adapted from the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [19]. The source of candidemia was classified by the attending physician. Central venous catheter (CVC) related candidemia was defined if the same *Candida* species was identified from both the tip culture of the intravascular device and peripheral blood culture in accordance with the guideline [20]. Gastrointestinal tract related candidemia was defined if the patients had evidence of intra-abdominal infection with identification of *Candida* species from a normally sterile area of the abdomen [21]. Urinary tract related candidemia was defined if the same *Candida* species was isolated from both urine culture and peripheral blood culture when the patient was noted to have evidence of urinary tract infection [17]. Abscess related candidemia was defined if the patient had localized pus formation with identification of the same *Candida* species seen from candidemia, which was walled-off from healthy tissue. If the source of candidemia could not be determined, it was classified as unknown. Antifungal treatment was considered as adequate if an antifungal agent with *in vitro* susceptibility was used according to the guideline [20]. Treatment outcomes were assessed in the followings: (1) clinical response defined as a complete or partial clinical response of attributable signs, symptoms, and radiographic findings of candidemia following the systemic antifungal therapy according to the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [22], (2) mycological response defined as eradication of candidemia

resulted in negative blood culture following the systemic antifungal treatment (mycological failure was defined as a failure to eradicate candidemia following the systemic antifungal treatment), (3) mortality defined as 30-day mortality after the diagnosis of candidemia.

Statistical analysis

Categorical variables were analysed by the Pearson $\chi 2$ test or Fisher's exact test. Continuous variables were presented as medians with inter-quartile ranges (IQRs). The student's t-test or Mann-Whitney U test was used for analysing continuous variables. Variables with *p*-value less than 0.2 in the comparison analysis were included in a multiple logistic regression analysis with backward selection to determine risk factors associated with septic shock as well as 30-day mortality of candidemia patients (Supplementary Table 1 and Table 3). The prediction model of 30-day mortality was created using risk factors with statistical significance ($p < .05$) or borderline significance ($p < .07$) identified from the multivariate analysis. The 30-day mortality rates of each significant factor were divided by 10 to obtain the factor scores. The Wilcoxon signed-rank test was used in the prediction model between survivors and non-survivors. The sensitivity and specificity of the prediction model were calculated. The performance of the prediction model was evaluated using the receiver operating characteristics (ROC) curve with a calculation of the area under the curve (AUC). The Kaplan-Meier curves were used for survival analyses with the log-rank test in the followings: (1) between the candidemia patients with and without septic shock and (2) among different groups of 30-day mortality risk factor scores. A *p*-value $< .05$ was considered to be statistically significant. SPSS version 23.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses.

Results

Demographics and clinical characteristics

During the study period, a total of 126 patients who met the study criteria were included in the study. The overall incidence rate of candidemia cases in the ICU was 1.76 per 1000 ICU admission-days, which showed an increasing trend over the study period (Figure 1). Demographics and clinical characteristics of the study population are shown in Table 1. The median age was 70 years (IQR 61 – 77 years), and 75 patients (59.5%) were male. The most common underlying comorbidity was malignancy

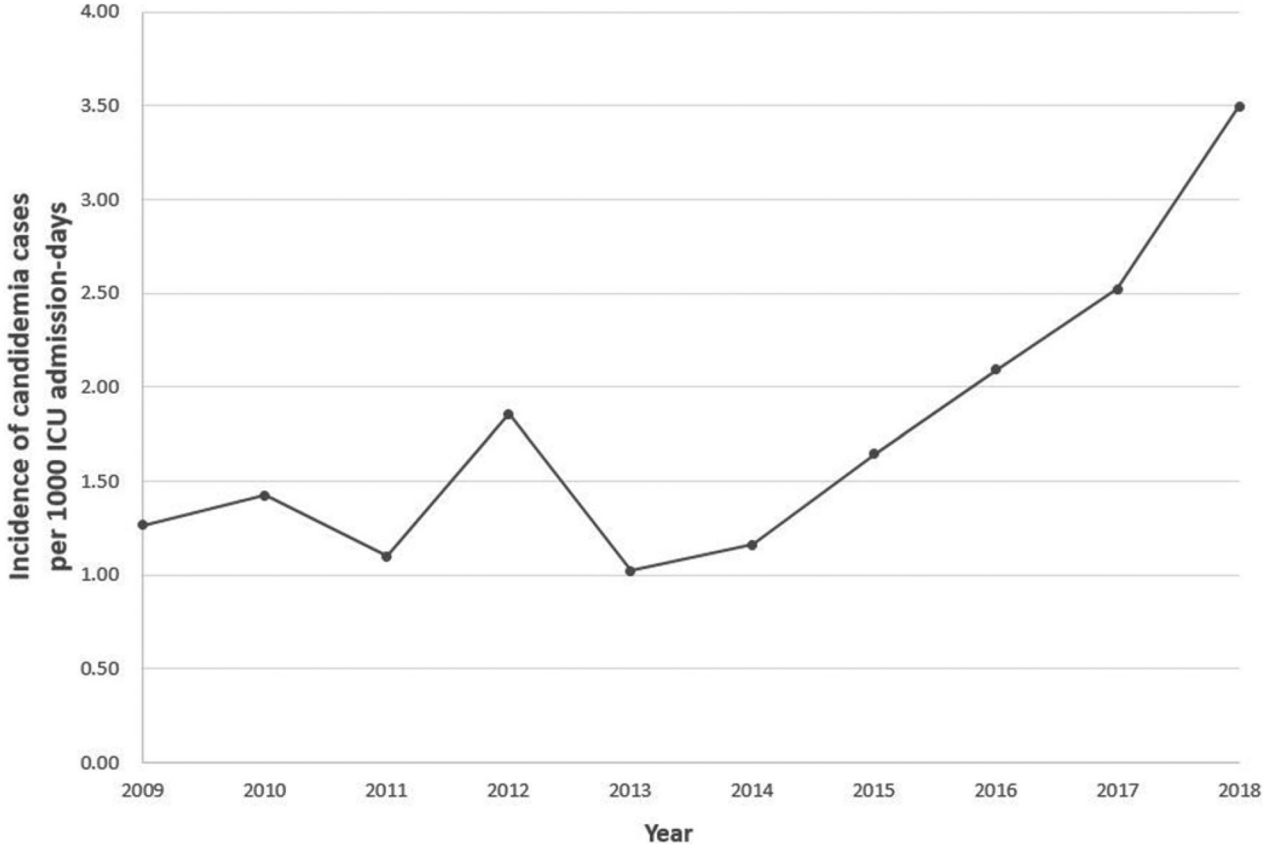

Figure 1. The incidence of candidemia in ICU during study periods.

Table 1. Demographic and clinical characteristics of the candidemia patients with and without septic shock.

	Total $N = 126$ (%)	No septic shock $N = 94$, (%)	Septic shock $N = 32$, (%)	p-value
Age, median (IQR[a])	70 (61 – 77)	70 (61 – 78)	70 (61 – 77)	.858
Sex, male	75 (59.5)	55 (58.5)	20 (62.5)	.691
Main comorbidities				
Charlson comorbidity index, median (IQR)	3 (2 – 6)	3 (2 – 6)	3 (2 – 4)	.719
Diabetes mellitus	44 (34.9)	32 (34.0)	12 (37.5)	.723
Malignancy	75 (59.5)	59 (62.8)	16 (50.0)	.204
Chronic central nervous system disease	30 (23.8)	19 (20.2)	11 (34.4)	.104
Chronic kidney disease	40 (31.7)	32 (34.0)	8 (25.0)	.343
Chronic liver disease	15 (11.9)	8 (8.5)	7 (21.9)	.059
Chronic pulmonary disease	16 (12.7)	11 (11.7)	5 (15.6)	.550
Chronic heart disease	54 (42.9)	39 (41.5)	15 (46.9)	.595
Clinical conditions				
Ventilation	35 (27.8)	23 (24.5)	12 (37.5)	.155
Urinary catheter	83 (65.9)	60 (63.8)	23 (71.9)	.407
Central venous catheter	95 (75.4)	69 (73.4)	26 (81.3)	.317
Recent surgery in the current admission	44 (34.9)	33 (35.1)	11 (34.4)	.940
Steroid use	57 (45.2)	42 (44.7)	15 (46.9)	.829
Parenteral nutrition	111 (88.1)	82 (87.2)	29 (90.6)	.759
Haemodialysis	15 (11.9)	10 (10.6)	5 (15.6)	.529
Neutropenia	16 (12.7)	10 (10.6)	6 (18.8)	.234
Chemotherapy	38 (30.2)	29 (30.9)	9 (28.1)	.772
Previous admission to intensive care unit within 3 months	46 (36.5)	32 (34.0)	14 (43.8)	.325
Previous use of antibiotics within 1 month	101 (80.2)	75 (79.8)	26 (81.3)	.858
Candida species of candidemia				
C. albicans	58 (46.0)	44 (46.8)	14 (43.8)	.764
C. parapsilosis	19 (15.1)	16 (17.0)	3 (9.4)	.397
C. tropicalis	30 (23.8)	22 (23.4)	8 (25.0)	.855
C. glabrata	15 (11.9)	11 (11.7)	4 (12.5)	1.000
C. krusei	2 (1.6)	1 (1.1)	1 (3.1)	.445
Other *Candida* species[b]	2 (1.6)	0 (0.0)	2 (6.3)	.063
Fluconazole resistance[c]	6 (6.3)	6 (9.4)	0 (0.0)	.173
Candidemia source				
Gastrointestinal tract	18 (14.3)	13 (13.8)	5 (15.6)	.776
Central venous catheter	74 (58.7)	53 (56.4)	21 (65.6)	.359
Urinary tract	13 (10.3)	13 (13.8)	0 (0.0)	.038
Abscess	1 (0.8)	1 (1.1)	0 (0.0)	1.000
Others or unknown	20 (15.9)	14 (14.9)	6 (18.8)	.606
Length of hospital stay in ICU, median days (IQR)	33 (16 – 39)	34 (17 – 39)	31 (17 – 39)	.692

[a]IQR, interquartile range.
[b]Other species, other *candida* species including *C. haemulonii* and *C. lustaniae*.
[c]Data available for 64 cases of no septic shock patients and 31 cases of septic shock patients.

(59.5%), followed by chronic heart disease (42.9%), diabetes mellitus (34.9%), and chronic kidney disease (31.7%). The majority of the patients had CVC (75.4%), urinary catheter (65.9%), receipt of total parenteral nutrition (88.1%), and previous use of antibiotics within 1 month (80.2%). Other clinical conditions included steroid use (45.2%), chemotherapy (30.2%), recent surgery in the current hospital admission (34.9%), ventilation (27.8%), and haemodialysis (11.9%). As for *Candidia* species of candidemia, the most frequently isolated species was *C. albicans* (46.0%), followed by *C. tropicalis* (23.8%), *C. parapsilosis* (15.1%), and *C. glabrata* (11.9%). Fluconazole resistance among *Candida* species was low (6.3%). The most prevalent source of candidemia was CVC (58.7%).

Factors associated with septic shock and treatment outcomes

Among the candidemia patients, the patients with septic shock (32 patients, 25.4%) were compared with those without septic shock (94 patients, 74.6%). These are shown in Table 1. There were no significant differences regarding age, sex, Charlson comorbidity index, comorbidities, clinical conditions, distribution and fluconazole resistance of *Candida* species of candidemia, and length of hospital stay in ICU between the groups of patients with and without septic shock. However, there were more patients who had chronic liver disease in the group of septic shock patients with borderline significance (21.9% vs. 8.5%, $p = .059$). In contrast, urinary tract related candidemia was less common in the group of septic shock patients (0.0% vs. 13.8%, $p = .038$). In the multivariate analysis, chronic liver disease (odds ratio [OR] 3.372, 95% confidence interval [CI] 1.057–10.057, $p = .040$) was independently associated with the development of septic shock in the candidemia patients (Supplementary Table 1). Regarding management, the mean CVC removal time after blood culture positivity was 4.7 days (IQR, 2−6 days). There was no difference regarding the mean CVC removal time after blood

culture positivity (4.2 days vs. 6.1 days, $p = .119$) and the rate of removal of CVC before antifungal treatment (27.5% vs. 30.8%, $p = .755$) in the candidemia patients without septic shock and with septic shock, respectively (Table 2). The source control of candidemia, defined as central venous catheter removal within 48 h after blood culture positivity, was similar between the patients without septic shock and with septic shock (77.1% vs. 84.0%, $p = .470$). Approximately half of the patients had initiation of antifungal treatment $>$ 48 h from onset of candidemia symptoms and blood culture sample; 46.8% and 50.0% for the patients without septic shock and with septic shock, respectively, without a difference ($p = .755$). The median length of ICU stay was 33 days, and the median antifungal treatment duration was 13 days. Although there was no significant difference in terms of antifungal treatment duration and adequate antifungal treatment between the two groups, there was a difference in the use of the antifungal agent. While fluconazole was used more frequently in the patients without septic shock (64.9% vs. 43.8%, $p = .035$), echinocandins were used more often in the patients with septic shock (46.9% vs. 25.5%, $p = .024$). The rates of clinical response (21.9% vs. 58.5%, $p < .001$) and mycological response (67.7% vs. 86.2%, $p = .022$) were significantly lower in the patients with septic shock. In addition, the 30-day mortality was significantly higher in the patients with septic shock (59.4% vs. 27.7%, $p = .001$), which was also demonstrated by the Kaplan-Meier curves with the log-rank test ($p = .001$) (Figure 2).

Factors associated with 30-day mortality and prediction model

We compared the candidemia patients who died at 30 days (45 patients, 35.7%) with those who survived (81 patients, 64.3%) to investigate risk factors associated with 30-day mortality (Table 3). In the comparison analysis, there were no significant differences in terms of demographics, distribution and fluconazole resistance of *Candida* species of candidemia, the length of ICU stay before blood culture positivity, the mean time of CVC insertion after ICU admission, and source of candidemia. Regarding management, there was no difference regarding the mean CVC removal time after blood culture positivity (4.5 days vs. 5.1 days, $p = .636$) in the survivors and non-survivors of candidemia patients, respectively (Table 3). The source control of candidemia, defined as central venous catheter removal within 48 h after blood culture positivity, was similar between the survivors and non-survivors (75.0% vs. 85.7%, $p = .217$). However, there were significantly more patients in the non-survival group who had these followings than those in the survival group: higher Charlson comorbidity index $\geq$ 3 (73.3% vs. 48.1%, $p = .006$), malignancy (71.1% vs. 53.1%, $p = .048$), chronic liver disease (20.0% vs. 7.4%, $p = .036$), haemodialysis (22.2% vs. 6.2%, $p = .008$), neutropenia

Table 2. Treatment-related variables and outcomes in the candidemia patients with and without septic shock.

	Total $N = 126$ (%)	No septic shock $N = 94$, (%)	Septic shock $N = 32$, (%)	*p*-value
Other management				
The mean CVC removal time after blood culture positivity, days (IQR)[a]	4.7 (2 – 6)	4.2 (2 – 5)	6.1 (2 – 9)	.119
CVC removal within 48 h after blood culture positivity[b]	75 (78.9)	54 (77.1)	21 (84.0)	.470
Removal of central venous catheter before antifungal therapy[c]	27 (28.4)	19 (27.5)	8 (30.8)	.755
Antifungal treatment				
Initiation of antifungal treatment $>$ 48 h from onset of candidemia symptoms and blood culture sample	60 (47.6)	44 (46.8)	16 (50.0)	.755
Fluconazole	75 (59.5)	61 (64.9)	14 (43.8)	.035
Voriconazole	1 (0.8)	1 (1.1)	0 (0.0)	1.000
Echinocandins[d]	39 (31.0)	24 (25.5)	15 (46.9)	.024
Amphotericin B	11 (8.7)	8 (8.5)	3 (9.4)	1.000
Antifungal treatment duration, median days (IQR[e])	13 (6–16)	13 (7–16)	10 (4 – 17)	.337
Adequate antifungal treatment[f]	89 (97.8)	58 (96.7)	31 (100.0)	.546
Clinical response	62 (49.2)	55 (58.5)	7 (21.9)	$<$.001
Mycological response[g]	102 (81.6)	81 (86.2)	21 (67.7)	.022
Mortality day 30 after diagnosis of candidemia	45 (35.7)	26 (27.7)	19 (59.4)	.001

[a]Data available for 70 cases of survivor patients and 25 cases of non-survival patients,.
[b]Data available for 70 cases of survivor patients and 25 cases of non-survivor patients,.
[c]Removal of central venous catheter before antifungal therapy, data calculated for 69 cases of no septic shock and 26 cases of septic shock patients with central venous catheter placement.
[d]Echinocandins including micafungin, caspofungin, and anidulafungin,.
[e]IQR, interquartile range,.
[f]Data available for 60 cases of no septic shock patients and 31 cases of septic shock patients.
[g]Data available for 94 cases of no septic shock patients and 31 cases of septic shock patients.

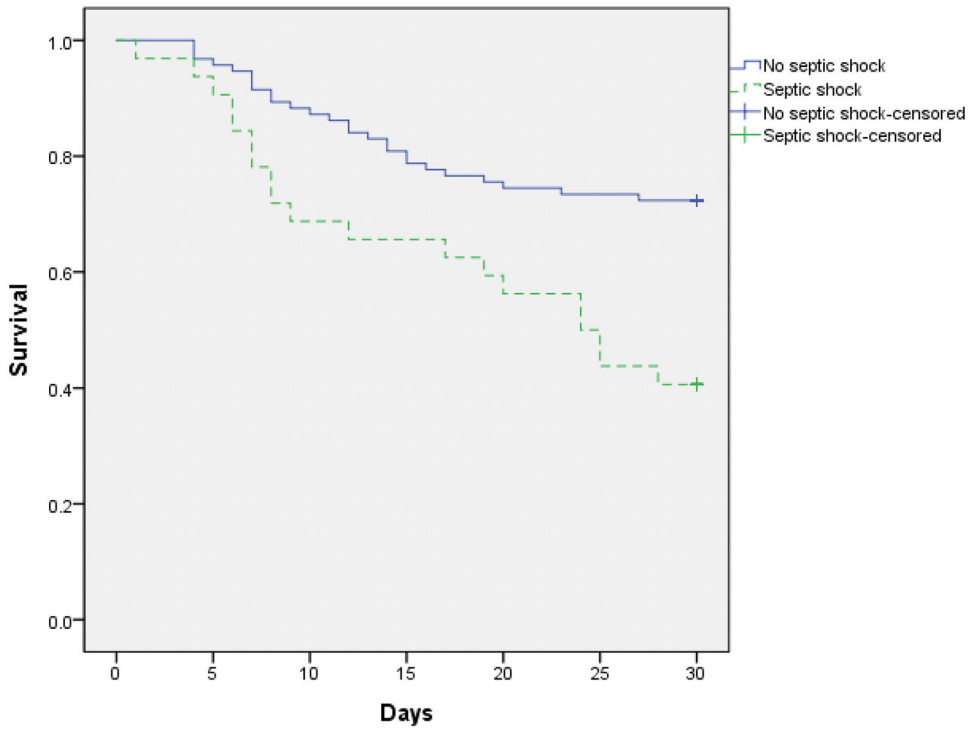

Figure 2. Thirty-day mortality of candidemia patients stratified by the presence of no septic shock and septic shock. Thirty-day mortality of the candidemia patients with no septic shock (27.7%) and septic shock (59.4%), log rank test, $p = .001$

(24.4% vs. 6.2%, $p = .003$), and chemotherapy (46.7% vs. 21.0%, $p = .003$). Although there was no difference regarding the use of the antifungal agent for candidemia treatment between the two groups, the prevalence of septic shock attributable to candidemia (42.2% vs. 16.0%, $p = .001$) and mycological failure (45.5% vs. 3.7%, $p < .001$) was significantly higher in the non-survivor group (Table 3). The multivariate analysis demonstrated that malignany (OR 8.251, 95% CI 2.227 − 30.573, $p = .002$), haemodialysis (OR 8.479, 95% CI 1.801 − 39.924, $p = .007$), mycological failure (OR 29.675, 95% CI 7.012 − 125.578, $p < .001$), and septic shock (OR 3.980, 95% CI 1.238 − 12.796, $p = .020$) were independently associated with 30-day mortality. Chronic liver disease (OR 3.605, 95% CI 0.913 − 14.227, $p = .067$) was found to have borderline significance (Table 3). Therefore, these five risk factors were used for creating the scoring tool for the prediction model. The 30-day mortality rates of each factor were divided by 10 to obtain the mortality risk factor scores (Table 4). The mortality risk factor scores were added for each patient. A ROC curve based on the mortality risk factor scores had an AUC of 0.862 (95% CI 0.797 − 0.927, $p < .001$) for the prediction model of 30-day mortality. The ideal threshold score of 7 was identified from the ROC curve with a sensitivity of 82.2% and a specificity of 82.7% (Figure 3). Furthermore, based on the mortality risk factor scores, three prognostic groups were designated: < 7 points group, 7–13 points group, and ≥ 14 points group. There were significant differences in terms of the 30-day mortality rates of these three groups: 10.7%, 65.6%, and 84.2%, respectively (Figure 4, $p < .001$).

Discussion

Our study demonstrated that the incidence of septic shock among candidemia patients in the ICU was 25.4%. Since there have been few studies focussing on the incidence of septic shock according to the Sepsis-3 definition [19] among candidemia patients in the ICU, the results of our study could further contribute to the knowledge of septic shock. Previously, the incidence of septic shock has been reported to have a range of 11%−49% in several studies conducted among general populations of patients diagnosed with candidemia [5,13,23–25]. Among them, a higher rate of septic shock incidence (49%) among candidemia patients was reported from a retrospective case-control study [25] than those of our study. On the other hand, there was a similar rate of septic shock incidence (30%) from a study of prospective cohorts [13] when compared to ours. Differences in the incidence of septic shock may be

Table 3. Comparison analysis of the candidemia patients for risk factors for 30-day mortality.

		Univariate			Multivariate[a]	
	Total $N = 126$ (%)	Survivor $N = 81$, (%)	Non-survivor $N = 45$, (%)	*p*-value	OR[b] (95% CI[c])	*p*-value
Age, median (IQR[d])	70 (61 – 77)	71 (62 – 79)	70 (57 – 76)	.359		
Sex, male	75 (59.5)	50 (61.7)	25 (55.6)	.499		
Main comorbidities						
Charlson comorbidity index ≥3	72 (57.1)	39 (48.1)	33 (73.3)	.006		
Malignancy	75 (59.5)	43 (53.1)	32 (71.1)	.048	8.251 (2.227–30.573)	.002
Chronic liver disease	15 (11.9)	6 (7.4)	9 (20.0)	.036	3.605 (0.913–14.227)	.067
Clinical conditions						
Recent surgery in the current admission	44 (34.9)	33 (40.7)	11 (24.4)	.066		
Steroid use	57 (45.2)	32 (39.5)	25 (55.6)	.083		
Parenteral nutrition	111 (88.1)	68 (84.0)	43 (95.6)	.054		
Haemodialysis	15 (11.9)	5 (6.2)	10 (22.2)	.008	8.479 (1.801–39.924)	.007
Neutropenia	16 (12.7)	5 (6.2)	11 (24.4)	.003		
Chemotherapy	38 (30.2)	17 (21.0)	21 (46.7)	.003		
Candida species of candidemia						
C. albicans	58 (46.0)	33 (40.7)	25 (55.6)	.110		
C. parapsilosis	19 (15.1)	15 (18.5)	4 (8.9)	.148		
C. glabrata	15 (11.9)	12 (14.8)	3 (6.7)	.176		
Other *Candida* species[e]	2 (1.6)	0 (0.0)	2 (4.4)	.126		
Candidemia source						
Central venous catheter	74 (58.7)	44 (54.3)	30 (66.7)	.177		
Urinary tract	13 (10.3)	11 (13.6)	2 (4.4)	.134		
The mean time of hospitalization in ICU, days (IQR)	33 (16 – 39)	32 (18 – 38)	36 (14 – 40)	.444		
The length of ICU stay before blood culture positivity, mean days (IQR)	25 (9 – 29)	22 (7 – 27)	30 (11 – 38)	.279		
Other management						
The mean CVC duration after ICU admission, days (IQR)[f]	23 (10 – 22)	22 (10– 22)	25 (10– 23)	.724		
The mean CVC removal time after blood culture positivity, days (IQR)[g]	4.7 (2 – 6)	4.5 (2 – 5)	5.1 (2 – 7)	.636		
CVC removal within 48 h after blood culture positivity[g]	75 (59.5)	45 (75.0)	30 (85.7)	.217		
Removal of central venous catheter before antifungal therapy[h]	27 (28.4)	19 (31.7)	8 (22.9)	.358		
Antifungal treatment						
Initiation of antifungal treatment > 48 h from onset of candidemia symptoms and blood culture sample	60 (47.6)	43 (53.1)	17 (37.8)	.099		
Fluconazole	75 (59.5)	52 (64.2)	23 (51.1)	.152		
Echinocandins[i]	39 (31.0)	22 (27.2)	17 (37.8)	.217		
Adequate antifungal treatment[j]	89 (97.8)	58 (98.3)	31 (96.9)	1.000		
Septic shock	32 (25.4)	13 (16.0)	19 (42.2)	.001	3.980 (1.238–12.796)	.020
Mycological response[k]	102 (81.6)	78 (96.3)	24 (54.5)	<.001		
Mycological failure	23 (18.4)	3 (3.7)	20 (45.5)		29.675 (7.012–125.578)	<.001

[a]In the multivariate logistic regression model, a backward (LR) selection approach was adopted,.
[b]OR, odds ratio.
[c]CI, confidence interval.
[d]IQR, interquartile range,.
[e]Other species, other *candida* species including *C. haemulonii* and *C. lustaniae*.
[f]The mean time of central venous catheter insertion after ICU admission, data calculated for 52 cases of survivor patients and 32 cases of non-survivor patients,.
[g]Data available for 60 cases of survivor patients and 35 cases of non-survivor patients.
[h]Removal of central venous catheter before antifungal therapy, data calculated for 60 cases of survivor patients and 35 cases of non-survivor patients with central venous catheter placement.
iEchinocandins including micafungin, caspofungin, and anidulafungin,.
[j]Data available for 59 cases of survivor patients and 32 cases of non-survivor patients,.
[k]Data available for 81 cases of survivor patients and 44 cases of non-survivor patients,.

Table 4. Thirty day-mortality rates of the factors on the multivariate logistic regression analysis and the corresponding factor scores.

Prognostic factor	Thirty day-mortality rate (%)	Factor score
Malignancy	42.7	4
Chronic liver disease	60.0	6
Haemodialysis	66.7	7
Mycologic failure[a]	87.0	9
Septic shock	59.4	6

[a]Data available for 81 cases of survivor patients and 44 cases of non-survivor patients.

explained by the differences in underlying comorbidities. Our patients' Charlson comorbidity index score was similar to a study of prospective cohorts [13], yet lower than that of a retrospective case-control study [25]. As a previous study showed that increased Charlson comorbidity index was associated with progression to septic shock [26], our results may reflect the importance of underlying comorbidities as one of the crucial factors regarding the incidence of septic shock in the cohort of candidemia patients.

Unlike a previous study [13], which showed that older age and an abdominal source of the candidemia infection were significant variables associated with septic shock among candidemia patients, our study did not

reveal significance in these variables. Differences in demographics and clinical conditions might have led to different results in our study as there was a higher prevalence of older age and abdominal surgery in our cohort of candidemia patients compared to a previous study [13,27]. However, our study demonstrated that chronic liver disease was a significant factor associated with the development of septic shock among candidemia patients in the ICU. It is well known that the liver plays an essential regulatory role in sepsis, and pre-existing liver dysfunction is a risk factor for the development of sepsis [28]. Recent studies also showed that chronic liver disease was one of the risk factors associated with mortality among candidemia patients [17,29]. Therefore, extrapolating from these data further supports our result of chronic liver disease as a significant factor associated with the development of septic shock among candidemia patients in the ICU.

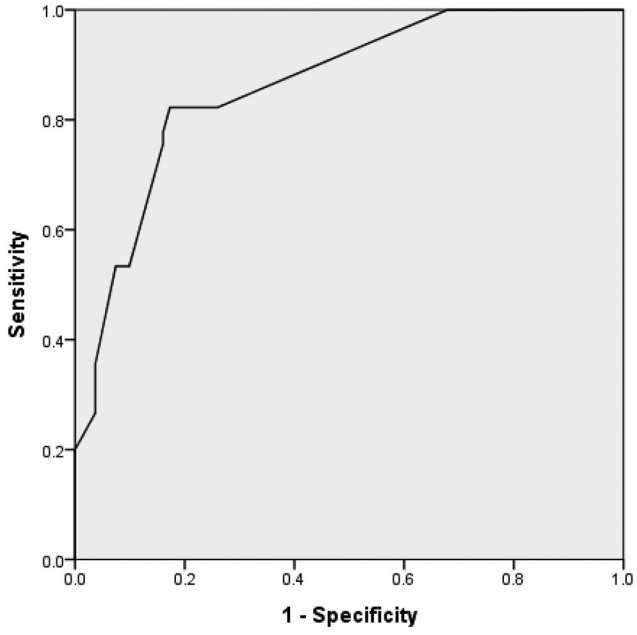

Figure 3. Receiver operating characteristic curve for the prediction model of thirty-day mortality of candidemia patients. Area under the curve of 0.862 and risk factor scores of 7 was associated with a sensitivity of 82.2% and a specificity 82.7% for the thirty-day mortality.

Previous studies reported the mortality rates were approximately 60% and 20%−40% for candidemia patients with septic shock and without septic shock, respectively [25,29–33]. In line with these studies, our study showed that the 30-day mortality rate was more remarkable for candidemia patients in the ICU with septic shock than those without septic shock (59.4% vs. 27.7%), reaffirming high mortality in this subset of patients. Regarding risk factors for 30-day mortality, our results were in agreement with previous studies, in which underlying comorbidities (malignancy [34,35] and chronic liver disease [36]) and clinical conditions

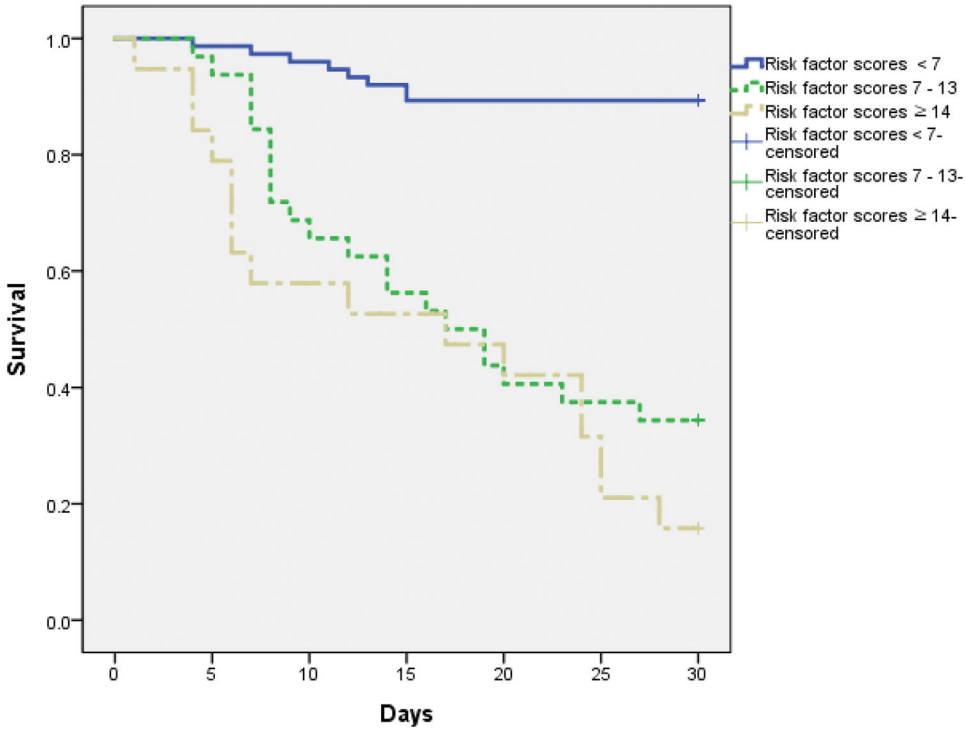

Figure 4. Thirty-day mortality of candidemia patients stratified by the mortality risk factor scores. Thirty-day mortality of the candidemia patients with the mortality risk factor scores < 7 (10.7%), 7–13 (65.6%), and ≥ 14 (84.2%), log rank test, $p < .001$

(haemodialysis [16,36], septic shock [23,37,38], and mycological failure [39]) were identified as risk factors for mortality in candidemia patients. In addition, an unmeasured variable of the impaired immune response from underlying comorbidities and clinical condition [40–42] might have contributed to an increased risk of mortality. Based on risk factors for 30-day mortality, the prediction model of 30-day mortality was created in the present study. As a cut-off value of the mortality risk score of 7 was identified from the prediction model with the sensitivity of 82.2% and specificity of 82.7%, candidemia patients in the ICU with the mortality risk score <7 were associated with an observed 30-day mortality rate of 10.7%. However, candidemia patients with higher mortality risk scores had higher rates of 30-day mortality (score $7-13$ with a 30-day mortality rate of 65.6% and score $\geq$ 14 with a 30-day mortality rate of 84.2%). Therefore, our prediction model of 30-day mortality would be useful in assessing the probability of 30-day mortality among candidemia patients in the ICU.

A recent retrospective study reported that ICU length of stay before candida BSI and CVC duration were significant risk factors associated with 28-day mortality of candidemia patients [43]. However, our study did not show the significance in these variables as there were no differences in terms of these variables between survivors and non-survivors in the study. There have been considerable variation in the timing of identification of candidemia in relation to the length of ICU stay as a mortality risk factor in the literature [44,45]. Also, previous studies showed that the removal of CVC might be more critical than the duration of CVC itself on the candidemia mortality [46,47]. While ICU length of stay before candida BSI and CVC duration could be factors associated with mortality in certain types of clinical setting, other factors might have influenced mortality in our study due to differences in clinical characteristics of the candidemia study patients.

CVC removal was the effective source control measure that could be performed in candidemia patients in the ICU [43]. The current guideline recommends that CVC should be remove as early as possible in the course of candidemia [20]. Previous studies evaluated that the adequate source control of candidemia as defined CVC removal within 48 h after blood culture positivity [43,48]. Although the mean time of CVC removal after culture positivity as 4.7 days (IQR, 2–6 days) in our study, most of patients (85.7% of survivors and 75% of non-survivors) removed CVC within 48 h after culture positivity. There has been a paucity of data on the appropriate time to remove CVC after candidemia. One retrospective cohort study has evaluated the effect of CVC removal time in candidemia patients. In this study, CVC removal itself was associated with 30-day mortality rather than the timing of CVC removal [46]. Also, another recent study reported that adequate early CVC removal may improve the survival of patients with candidmia with low Charlson comorbidities index [47]. In real clinical setting, early removal of CVC in all patients may be challenging due to the fact that candidemia patients may be critically ill requiring CVC [49]. Therefore, more studies reflecting the real world clinical setting are needed to assess the impact of the timing of source control of candidemia patients.

The guideline recommends antifungal treatment for 2 weeks after candidemia eradication in blood cultures [20]. Our study reported that the median antifungal treatment duration was 13 days. However, more than half of the patients (59.5%) received treatment for more than 2 weeks. Recent retrospective study reported that 47% of the survivors received antifungal treatment for $\geq$2 weeks compared to only 37% of the non-survivors. The remaining non-survivors died earlier (51%) [29]. However, our results shown that the patients treated antifungal agents for more than 2 weeks were similar between the survivors (59.3%) and non-survivors (60%), respectively, without difference. Forty percentage of the non-survivors died before antifungal therapy conclusion. These results suggest that overall short duration of antifungal treatment reported in our study might be due to occurrence of death before antifungal therapy conclusion. In addition, these results also imply that the antifungal treatment duration recommended in the guideline might be difficult to apply with limited generalizability depending on the real world clinical setting [50].

Of interest, antifungal treatment was not significantly different between the patients with and without 30-day mortality despite the more frequent use of echinocandins in the patients with septic shock in our study. A high percentage of adequate antifungal treatment (overall 97.8%; 96.9% and 98.3% in the patients with and without 30-day mortality, respectively, $p = 1.000$) and low rate of fluconazole resistance among *Candida* species of candidemia (overall 6.3%; 5.7% and 6.7% in the patients with and without 30-day mortality, respectively, $p = 1.000$) in our patients may explain these findings. Furthermore, echinocandins are primarily recommended for the treatment of candidemia according to the guideline [20]. Also, there has been an increased utilization of

echinocandins in the ROK following expanded national health insurance coverage of echinocandins for critically ill patients diagnosed with candidemia in 2014 [51]. Therefore, our results of the more frequent use of echinocandins in the candidemia patients with septic shock may indicate the indirect effects resulted from incorporation of the guideline [20] into clinical practice along with expanded national health insurance coverage of echinocandins. However, there has been controversy regarding the association of a specific antifungal agent for treatment with improved outcomes. In a multicenter study [52], fluconazole was not associated with increased 30-day mortality compared to echinocandins among candidemia patients, even among patients with septic shock. However, an association of an echinocandin treatment with decreased mortality was reported from a study using a patient-level quantitative review of randomized trials [53]. Thus, more data with definitive real-world clinical evidence are needed to determine an association between specific antifungal agents and treatment outcomes, including mortality.

Our study has several limitations, due to a single-centre study with relatively small sample size. We could not include other core elements of candidemia management, such as adequate source control in the risk factor analyses of septic shock and 30-day mortality. Also, there was some limited information on antifungal susceptibility data as it became available in the later study period (fluconazole, voriconazole, and amphotericin from 2011 and echinocandins from 2013) despite the low probability of antifungal resistance in the earlier study period. Therefore, unintended selection bias from a retrospective study design and confounding effects from unmeasured variables might have affected our analyses. However, we used constant definitions and multivariate logistic regression analysis to minimize potential bias. Additionally, our study results might not be applicable to the clinical setting, where there is a higher rate of fluconazole resistance or echinocandin resistance. Thus, future prospective studies with the inclusion of more centres and larger numbers of patients may be required for further assessment of the reproducibility of our results and validation of the predictive model.

Conclusions

Adult candidemia patients in the ICU who have chronic liver disease may be at higher risk for the development of septic shock. Furthermore, our results suggest that malignancy, chronic liver disease, haemodialysis, mycological failure, and septic shock may be significant factors associated with 30-day mortality. Also, a predictive model for 30-day mortality based on the mortality risk factors may be useful for a clinical assessment for risk stratification.

Ethics approval and consent to participate

This study was approved by the institutional review board at the Korea University Anam Hospital (IRB Number 2018AN0440).

Consent for publication

Not applicable

Author contributions

JH Kim and JW Suh designed the study. All authors contributed to collection of data. JW Suh and JH Kim performed the analysis. The manuscript was drafted by JW Suh, and JH Kim revised the manuscript. All authors reviewed and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

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