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ORIGINAL ARTICLE

Candidemia in hospitalized cirrhotic patients with bloodstream infection: A retrospective analysis and brief summary of published studies

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Abstract

Background: Candidemia is a life-threatening condition; however, the predictive markers for candidemia and mortality are inadequate in cirrhotic patients. This study was conducted to propose candidate predictors for the occurrence of candidemia and 30-day mortality in hospitalized cirrhotic patients with bloodstream infection (BSI) and review the related literature.

Methods: Cirrhotic patients with BSI between January 2011 and March 2020 were screened from the databank of a medical center and eligible patients were enrolled. Patients were separated into candidemia and bacteremia groups according to the results of blood cultures. Baseline characteristics, clinical presentation, and biochemistry data were collected at this time, as were microbiological data, medical management, use of antimicrobial agents, and outcome of the patients. The parameters and 30-day mortality were compared between candidemia and bacteremia groups. A combination of the MeSH terms and text terms related to candidemia and cirrhosis was searched in the electronic databases.

Results: Four hundred and sixty cirrhotic patients with BSI were enrolled. Thirty-five patients with candidemia (7.6%) were identified. Nosocomial infection, intensive care unit (ICU) admission, antibiotics exposure ≥14 days, white cell count >10 K/mm^3, and model for end-stage liver disease (MELD) score >24 were associated with candidemia. The 30-day mortality was 65.7% in the candidemia group and 37.9% in the bacteremia group (p = 0.001). Nosocomial infection, ICU admission, hepatoma, hepatic encephalopathy, international normalized ratio ≥1.2, platelet ≤150 K/mm^3, estimated glomerular filtration rate <60 mL/min/1.73m^2, and MELD score >24 were associated with 30-day mortality. Six studies were identified. The results were consistent with our findings regarding low incidence of candidemia, and relevant risk factors are listed.

Conclusion: Candidemia had low incidence but high mortality in hospitalized cirrhotic patients with BSI. New predictors were proposed for the occurrence of candidemia and 30-day mortality in these patients.

Keywords: Bloodstream infection; Candidemia; Cirrhosis

1. INTRODUCTION

Cirrhosis may lead to immune system dysfunction including abnormalities of immune function, immunodeficiency, and systemic inflammation.[1] Patients with cirrhosis are susceptible to bloodstream infection (BSI) with the progression of the degree of liver dysfunction.[2] BSI could be present in 4 to 21% of the hospitalized patients with cirrhosis.[2,3] Cirrhotic patients with BSI are 2.4- to 6.3-fold more likely to die within 30-days compared to noncirrhotic patients with similar infection.[4]

Admission bacterial infection is associated with fungal infection development in patients with cirrhosis,[5] and fungal infection is described as an emerging problem associated with delayed diagnosis and high fatality rates.[6] The prevalence rate is about 5% in hospitalized patients with cirrhosis,[5] although the frequency of invasive fungal infection is low in patients with end-stage liver disease but delayed treatment might contribute to a high mortality rate.[7] Candidemia is the most frequent manifestation of invasive fungal infection and is reported as the fourth most common BSI in the intensive care unit (ICU) and the seventh to tenth most common BSI in population-based studies.[8] The mortality rate of candidemia is higher than bacteremia in patients with cirrhosis.[9,10] Although there is an increasing

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incidence of candidemia among patients with cirrhosis, the incidence and characteristics of candidemia in patients with cirrhosis has been rarely analyzed.[9] The primary objective of the study, therefore, was to explore the incidence and independent predictors for the occurrence of candidemia in hospitalized patients with cirrhosis and BSI, with the secondary objectives to examine the independent predictors for 30-day mortality after the onset of BSI and to review the related literature in the electronic databases.

2. METHODS

2.1. Patient enrollment and definition

This retrospective study was conducted at Kaohsiung Veterans General Hospital, a medical center with a 1700-bed capacity providing both primary and tertiary referral care in southern Taiwan. All consecutive hospitalized patients with cirrhosis and BSI between January 2011 and March 2020 were considered and evaluated, with the inclusion criteria being: (1) patients aged equal to or more than 18 years, and (2) previous diagnosis of liver cirrhosis. The exclusion criteria included patients (1) being negative for blood culture, and (2) lacking sufficient clinical and biochemistry data.

The diagnosis of cirrhosis was established based on clinical, biochemical, and imaging studies including abdominal sonography, computed tomography, magnetic resonance imaging, or a liver biopsy. The severity of cirrhosis was assessed according to the model for end-stage liver disease (MELD) score.[11] BSI was defined as a positive result on microorganisms isolated from blood culture. Only one blood culture set grew coagulase-negative *Staphylococci,* but was considered as contamination of the blood culture. Candidemia was defined according to criteria of the Infectious Diseases Society of America.[12] Inappropriate antibiotic therapy was defined as lack of antibiotic use with adequate susceptibility according to the results of blood cultures.

2.2. Data collection

The following demographic data of each patient were collected from the hospital medical records: age, sex, concomitant diseases, clinical characteristics, laboratory examinations, use of antibiotics within 30 days before the onset of BSI, length of hospital and ICU stay, and 30-day mortality.

Bactec FX blood culture system (Becton Dickinson, Franklin Lakes, NJ, USA) was used for the culture of the specimen. BACTEC Plus Aerobic/F Culture Vials were used for the aerobic culture. BACTEC Lytic/10 Anaerobic/F Culture Vials were used for the anaerobic culture. *Candida spp*. was identified by the BACTEC Myco/F Lytic Culture Vials with the VITEK 2 YST ID card in conjunction with the VITEK 2 system. The interpretation of the isolated microorganism and susceptibility to antimicrobials followed the criteria by the Clinical and Laboratory Standards Institute (CLSI) breakpoints (CLSI M100-S19, 2009).[13]

2.3. Search of the literature

Two investigators (Y.-C.C. and W.-C.C.) searched in PubMed for relevant publications up to July 2021 with the combination of the MeSH terms and text terms as follows: ((“fungus”[MeSH Terms] OR “fungus”[All Fields] OR “fungemia”[MeSH Terms] OR “fungemia”[All Fields]) OR (“candida”[MeSH Terms] OR “candida”[All Fields] OR “candidemia”[MeSH Terms] OR “candidemia”[All Fields])) AND (“liver cirrhosis”[MeSH Terms] OR (“liver”[All Fields] AND “cirrhosis”[All Fields]) OR “liver cirrhosis”[All Fields] OR “cirrhosis”[All Fields]) AND “humans”[MeSH Terms] studies. The titles and abstracts generated by the search were reviewed, and those studies not meeting the selection criteria were excluded. Guidelines, review articles, editorials, commentaries, letters, and case reports were also excluded.

2.4. Statistical analysis

The baseline demographic data of the patients were compared between the candidemia group and the bacteremia group. Continuous variables with normal distribution were analyzed as mean and SD. Chi-square or Fisher’s exact test was used to compare the categorical data when appropriate. Independent Student’s t-test was used to compare the continuous variables with normal distributions. Mann-Whitney U test was used to compare the continuous variables without normal distributions. Univariate and stepwise logistic regression was used to examine the independent predictors for the occurrence of candidemia and 30-day mortality. The Stepwise regression within backwards selection process starts from a univariate analysis of the collected parameters. Any variable having a significant univariate test at a p-value of <0.10 was selected as a candidate for the multi-variate analysis.[14] The maximum value of the area under curve was selected to determine the optimal cutoff values of each parameter. Calibration curves were plotted to assess the regression, along with the Hosmer-Lemeshow test. A significant test statistic implied that the model was not perfectly calibrated. Kaplan-Meier estimation with a log-rank test was used to analyze the time of onset of BSI to mortality within 30 days in candidemia and bacteremia groups. Significance was defined as $p < 0.05$ for all two-tailed tests. All statistical analyses were performed using Statistical Analysis Software (SAS; version 9.4; SAS System for Windows) and the SPSS statistical software package, version 20.0 for Windows (SPSS Inc., Chicago, IL).

2.5. Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the hospital’s institutional review board (KSVGH21-CT3-18). Written informed consent was waived off because of the retrospective nature of the study.

3. RESULTS

Five thousand two hundred ninety-two patients with cirrhosis admitted to Kaohsiung Veterans General Hospital were initially evaluated during the study period. Four thousand seven hundred fifty-seven patients were excluded due to being negative for BSI, as were 75 patients due to having incomplete laboratory or clinical data. With 535 patients having BSI altogether, a total of 460 patients with BSI were eventually enrolled with 35 patients having candidemia and 425 patients having bacteremia (Fig. 1).

3.1.Demographic data of the patients

The demographic data of the candidemia group (n = 35) and the bacteremia group (n = 425) is shown in Table 1. The causes of BSI in the candidemia group patients were intra-abdominal infection (three patients), endoscopic procedure (two patients), urinary tract infection (three patients), spontaneous fungal peritonitis (seven patients), intra-abdominal abscess (two patients), pneumonia (three patients), catheterization (two patients), hallow organ perforation (one patient), cellulitis (one patient), cholangitis (one patient), surgery wound (five patients), and undetermined (five patients). The causes of BSI in the bacteremia group patients were intra-abdominal infection (33 patients),

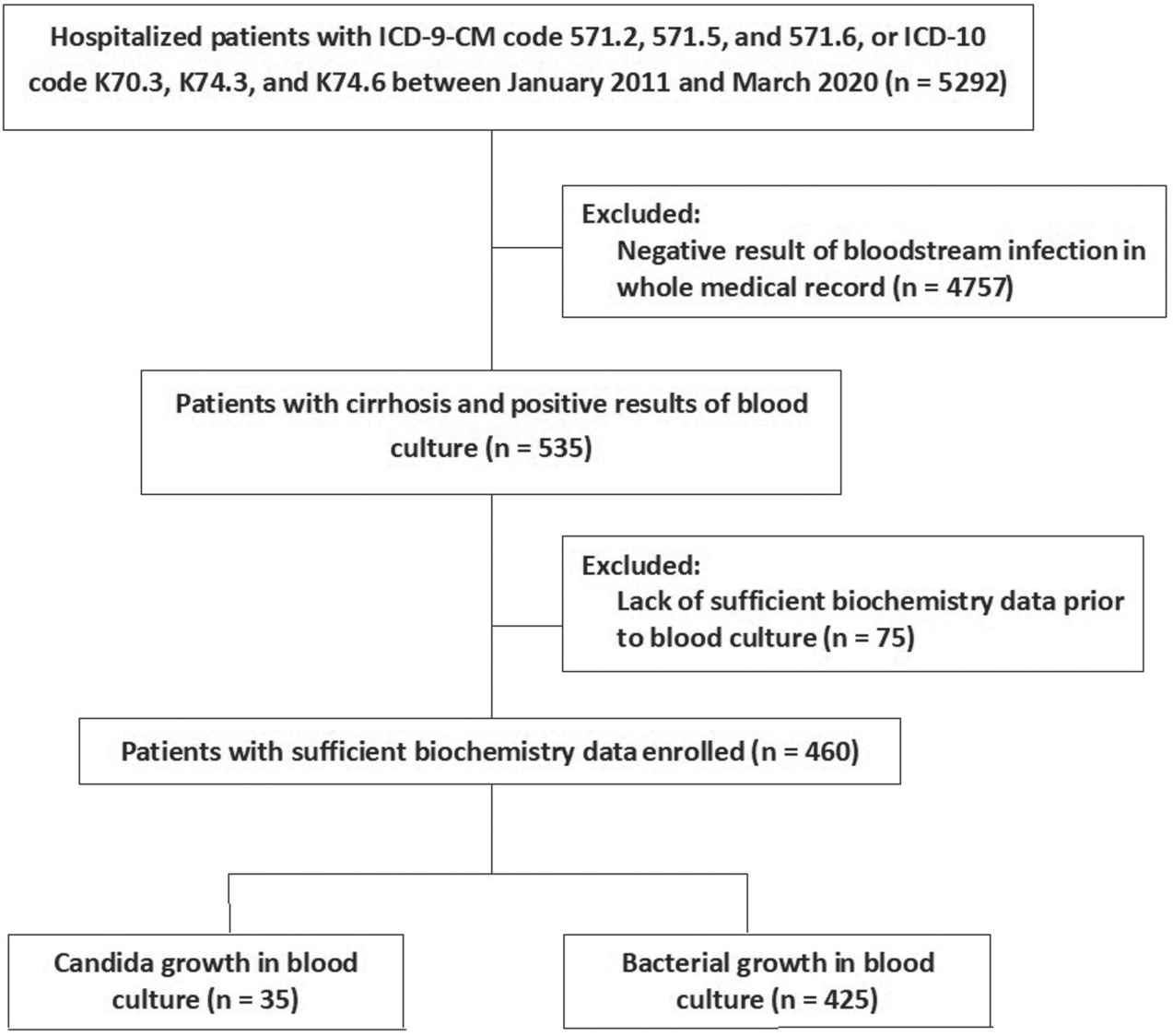

Fig. 1 Flowchart of the patients with cirrhosis and bloodstream infection.

endoscopic procedure (three patients), urinary tract infection (77 patients), spontaneous bacterial peritonitis (67 patients), meningitis (one patient), liver abscess (four patients), acute pyelonephritis abscess (three patient), renal abscess (two patients), breast abscess (one patient), pneumonia (49 patients), empyema (three patients), catheterization (three patients), cellulitis (11 patients), necrotizing fasciitis (seven patients), cholangitis (30 patients), surgery wound (seven patients), osteomyelitis (four patients), and undetermined (120 patients). The indications for central venous catheter (CVC) use in the candidemia group included difficult venous access (nine patients), total parenteral nutrition (TPN) use (six patients), and central venous pressure monitoring (three patients). The indications for CVC use in the bacteremia group included difficult venous access (30 patients), TPN use (seven patients), and central venous pressure monitoring (15 patients). The indications for TPN use in the candidemia group included prolonged bowel rest (five patients) and bowel obstruction (one patient). The indications for TPN use in the bacteremia group included prolonged bowel rest (three patients), bowel obstruction (two patients), gastrointestinal fistula (one patient), and severe malnutrition (one patient).

3.2. Predictive markers for the occurrence of candidemia and treatments for candidemia

The incidence of candidemia was 7.6% among patients with cirrhosis and BSI. No patient had concomitant candidemia and bacteremia. The microbial etiology distribution of BSI is shown in Table 2. Of the candidemia group, *Candida albicans* (42.9%) was the most common microorganism, followed by *C. tropicalis* (22.8%), *C. glabrata* (20.0%), *C. parapsilosis* (8.5%), *C. krusei* (2.9%), and other *Candida* species (2.9%). Of the bacteremia group, *Escherichia coli* (21.6%), *Klebsiella pneumoniae* (11.8%), *Streptococcus spp.* (7.1%), and *Staphylococcus aureus* (26.9%) accounted for most of the microbiological population.

Univariate logistic regression analysis showed that CVC use (odds ratio [OR]: 7.60, 95% confidence interval [CI]: 3.68-15.66,

Table 1

Baseline characteristics of patients with cirrhosis and bloodstream infection

	Total	Candidemia group	Bacteremia group	*p*
Variable	n = 460	n = 35	n = 425	
Age (y)[a]	66.1 ± 14.6	62.8 ± 16.2	66.4 ± 14.4	0.16
Sex				
Male	303 (65.9%)	20 (57.1%)	283 (66.6%)	0.26
Female	157 (34.1%)	15 (42.9%)	142 (33.4%)	
Comorbidity				
Hypertension	201 (43.7%)	13 (37.1%)	188 (44.2%)	0.42
Diabetes mellitus	133 (28.9%)	11 (31.4%)	122 (28.7%)	0.73
Hyperlipidemia	115 (25.0%)	6 (17.1%)	109 (25.6%)	0.26
Congestive heart failure	68 (14.8%)	3 (8.6%)	65 (15.3%)	0.28
HCC	125 (27.2%)	8 (22.9%)	117 (27.5%)	0.55
BCLC 0/A/B/C/D	14/34/25/31/21	0/3/1/4/0	14/31/24/27/21	
Etiology of cirrhosis				
Hepatitis B	286 (62.2%)	25 (71.4%)	261 (61.4%)	0.24
Hepatitis C	68 (14.8%)	4 (11.4%)	64 (15.1%)	0.56
Alcohol	134 (29.1%)	10 (28.6%)	124 (29.2%)	0.94
Nosocomial infection	209 (45.4%)	30 (85.7%)	179 (42.1%)	<0.001
CVC use	70 (15.2%)	18 (51.4%)	52 (12.2%)	<0.001
TPN use	13 (2.8%)	6 (17.1%)	7 (1.6%)	<0.001
Hepatic encephalopathy	121 (26.3%)	11 (31.4%)	110 (25.9%)	0.47
Grade I/II/III/IV	57/31/21/12	5/3/2/1	52/28/19/11	
Ascites	246 (53.5%)	17 (48.5%)	229 (53.9%)	0.54
Mild/moderate/severe		6/4/7	74/54/101	
Antibiotic exposure (d)[a]	8.9 ± 10.7	25.6 ± 15.7	7.6 ± 8.9	<0.001
Laboratory data				
Albumin (g/dL)[a]	2.7 ± 0.6	2.8 ± 0.6	2.7 ± 0.7	0.34
Total bilirubin (mg/dL)[a]	4.6 ± 6.4	6.2 ± 8.1	4.5 ± 6.3	0.13
PT (s)[a]	16.1 ± 9.3	18.2 ± 11.1	15.9 ± 9.2	0.17
INR[a]	1.5 ± 0.8	1.7 ± 1.0	1.5 ± 0.8	0.051
Creatinine (mg/dL)[a]	2.3 ± 2.0	2.4 ± 1.5	2.3 ± 2.1	0.87
eGFR (mL/min/1.73m^2)[a]	50.7 ± 37.3	42.5 ± 31.4	51.4 ± 37.7	0.18
Hemoglobin (g/dL)[a]	10.3 ± 2.3	9.2 ± 1.7	10.4 ± 2.3	0.002
Platelet (K/mm^3)[a]	128.2 ± 100.5	124.6 ± 142.2	128.5 ± 96.5	0.82
White cell count (K/mm^3)[a]	11.5 ± 7.5	14.7 ± 7.8	11.2 ± 7.5	0.009
MELD score[a]	18.7 ± 9.9	22.3 ± 11.3	18.5 ± 9.8	0.028
Child-Pugh class				0.42
A	161 (35.0%)	13 (37.1%)	148 (34.8%)	
B	149 (32.4%)	8 (22.8%)	141 (33.2%)	
C	150 (32.6%)	14 (40.0%)	136 (32.0%)	
ALBI score[a]	-1.2 ± 0.7	-1.2 ± 0.6	-1.2 ± 0.7	0.98
Variceal bleeding	45 (9.8%)	5 (14.3%)	40 (9.4%)	0.35
Ulcer bleeding	49 (10.7%)	4 (11.4%)	45 (10.6%)	0.78
Acute kidney injury	44 (9.6%)	6 (17.1%)	38 (8.9%)	0.13
Hepato-renal syndrome	45 (9.8%)	4 (11.4%)	41 (9.6%)	0.77
Length of stay (d)[a]	18.1 ± 35.7	39.2 ± 35.1	16.4 ± 35.2	<0.001
ICU admission	49 (10.7%)	21 (60.0%)	28 (6.6%)	<0.001
Length of ICU stay (d)[a]	6.2 ± 32.8	21.9 ± 31.9	4.9 ± 32.6	0.003
30-day mortality	188 (40.9%)	23 (65.7%)	165 (38.8%)	0.001

ALBI = albumin-bilirubin; BCLC = Barcelona Clinic Liver Cancer; BSI = bloodstream infection; CVC = central venous catheter; eGFR = estimated glomerular filtration rate; HCC = hepatocellular carcinoma; ICU = intensive care unit; INR = international normalized ratio; MELD = model for end-stage liver disease; PT = prothrombin time; TPN = total parenteral nutrition.

[a]The results of the continuous variables are expressed as mean ± SD.

p < 0.001), TPN use (OR: 12.34, 95% CI: 3.90-39.16, p < 0.001), nosocomial infection (NI) (OR: 8.25, 3.14-21.67, p < 0.001), antibiotics exposure ≥ 14 days (OR: 13.93, 95% CI: 6.27-30.97, p < 0.001), hemoglobin ≤ 10 g/dL (OR: 2.92, 95% CI: 1.37-6.23, p = 0.006), white cell count > 10 K/mm^3 (OR: 2.44, 95% CI: 1.18-5.03, p = 0.016), MELD score > 24 (OR: 2.77, 95% CI: 1.38-5.56, p = 0.004), and ICU admission (OR: 11.90, 95% CI: 5.38-26.36, p<0.001), were associated with candidemia (Table 3).

At stepwise logistic regression analysis, NI (adjusted OR [aOR]: 3.22, 95% CI: 1.03-10.2, p = 0.044), ICU stay (aOR: 5.52, 2.27-13.40, p < 0.001), antibiotics exposure ≥ 14 days (aOR: 8.00, 95% CI: 3.14-20.36), p < 0.001), white cell count > 10 K/mm^3 (aOR: 2.79, 95% CI: 1.18-6.61, p = 0.020), and MELD score > 24 (aOR: 3.45, 95% CI: 1.44-8.27, p = 0.005) were associated with candidemia (Table 4)

Thirty patients in the candidemia group (85.7%) received antifungal agents including micafungin (17%), anidulafungin (34.3%), fluconazole (31.4%), and flucytosine (2.8%). Five patients (14.3%) did not receive antifungal therapy because the blood cultures grew out fungus after the patients expired. Successful treatment of candidemia was achieved in 24

Table 2

Microbiology etiology distribution in inpatients with cirrhosis and bloodstream infection

Species	Candidemia group, n (%)	Bacteremia group, n (%)
Candida		
Candida albicans	15 (42.9)	
Candida tropicalis	8 (22.8)	
Candida glabrata	7 (20.0)	
Candida parapsilosis	3 (8.5)	
Candida krusei	1 (2.9)	
Other Candida species	1 (2.9)	
Gram-negative bacteria		
Escherichia coli		89 (20.9)
ESBL *Escherichia coli*		3 (0.7)
Klebsiella pneumoniae		47 (11.1)
ESBL *Klebsiella pneumonia*		3 (0.7)
Enterobacter spp.		15 (3.5)
Aeromonas spp.		14 (3.3)
Acinetobacter baumannii		14 (3.3)
Pseudomonas aeruginosa		13 (3.1)
Vibrio spp.		7 (1.6)
Citrobacter spp.		4 (0.9)
Serratia marcescens		3 (0.7)
Salmonella enteritidis spp.		5 (1.2)
Morganella morganii spp.		4 (0.9)
Elizabethkingia meningoseptica		2 (0.5)
Gram-positive bacteria		
Staphylococcus aureus		36 (8.5)
Staphylococcus epidermidis		7 (1.6)
Other *Staphylococcus spp.*		16 (3.8)
Streptococcus spp.		30 (7.1)
Enterococcus spp.		8 (1.9)
Coagulase-negative *Staphylococci*		62 (14.6)
Gram-positive bacilli		19 (4.5)
Listeria monocytogenes		3 (0.7)
Other species		21 (4.9)

ESBL = extended-spectrum β-lactamase.

Table 3

Univariate logistic regression analysis for candidemia in patients with cirrhosis (n = 460)

Variables	Beta	OR (95% CI)	*p*
Age	–0.017	0.98 (0.96-1.01)	0.16
Male sex	–0.402	0.67 (0.33-1.35)	0.26
Comorbidity			
Hypertension	–0.294	0.75 (0.37-1.52)	0.42
Diabetes mellitus	0.130	1.14 (0.54-2.39)	0.73
Hyperlipidemia	–0.511	0.60 (0.24-1.48)	0.27
Congestive heart failure	–0.655	0.52 (0.15-1.75)	0.29
HCC	–0.248	0.78 (0.35-1.77)	0.55
Hepatitis B	0.452	1.57 (0.74-3.36)	0.24
Hepatitis C	–0.318	0.73 (0.25-2.13)	0.56
Nosocomial infection	2.110	8.25 (3.14-21.67)	<0.001
CVC use	2.207	7.60 (3.68-15.66)	<0.001
TPN use	2.514	12.34 (3.90-39.16)	<0.001
Hepatic encephalopathy	0.272	1.31 (0.62-2.77)	0.48
Ascites	–0.341	0.71 (0.33-1.52)	0.38
Antibiotics exposure ≥ 14 d	2.634	13.93 (6.27-30.97)	<0.001
Laboratory data			
Albumin ≤ 3 g/dL	0.059	1.06 (0.51-2.23)	0.88
Total bilirubin ≥ 2 mg/dL	0.589	1.80 (0.88-3.72)	0.11
INR ≥ 1.2	0.724	2.07 (0.94-4.51)	0.07
Creatinine > 1 mg/dL	0.448	1.57 (0.63-3.88)	0.33
eGFR < 60 mL/min/1.73m^2	0.318	1.37 (0.63-3.01)	0.43
Hemoglobin ≤ 10 g/dL	1.072	2.92 (1.37-6.23)	0.006
Platelet ≤ 150 K/mm^3	0.208	1.23 (0.56-2.70)	0.60
White blood count > 10 K/mm^3	0.892	2.44 (1.18-5.03)	0.02
MELD score > 24	1.02	2.77 (1.38-5.56)	0.004
Child-Pugh class C	0.348	1.42 (0.70-2.87)	0.33
ALBI score grade 3	0.345	1.41 (0.67-2.96)	0.36
ICU admission	2.477	11.90 (5.38-26.36)	<0.001

ALBI = albumin-bilirubin; CI = confident interval; CVC = central venous catheter; eGFR = estimated glomerular filtration rate; HCC = hepatocellular carcinoma; ICU = intensive care unit; INR = international normalized ratio; MELD = model for end-stage liver disease; OR = odds ratio; PT = prothrombin time; TPN = total parenteral nutrition.

patients receiving micafungin (six patients, 17.1%), anidulafungin (eight patients, 22.9%), and fluconazole (10 patients, 28.5%).

3.3. Predictive markers for 30-day mortality

Twenty-three patients (65.7%) in the candidemia group and 161 patients (37.9%) in the bacteremia group died within 30 days after the onset of BSI (p = 0.001, Fig. 2). The causes of mortality in the candidemia group were candidemia (11 patients), liver failure (six patients), hepatorenal syndrome (three patients), multi-organ failure (two patients), and renal failure (one patient). The causes of mortality in the bacteremia group were sepsis (64 patients), liver failure (55 patients), hepatorenal syndrome (eight patients), hepatoma (14 patients), multi-organ failure (12 patients), infective endocarditis (one patient), and esophageal variceal bleeding (seven patients). Univariate analysis showed that CVC use (OR: 5.91, 95% CI: 3.68-15.66, p < 0.001), TPN use (OR: 12.36, 95% CI: 3.90-39.16, p < 0.001), hepatic encephalopathy (OR: 2.26, 95% CI: 0.62-2.77, p < 0.001), ascites (OR: 1.69, 95% CI: 0.33-1.52, p = 0.009), NI (OR: 2.46, 95% CI: 1.68-3.61, p < 0.001), antibiotics exposure ≥ 14 days (OR: 2.36, 95% CI: 6.27-30.97, p < 0.001), albumin ≤ 3 g/dL (OR: 2.06, 95% CI: 1.35-3.14, p = 0.001), total bilirubin ≥ 2 mg/dL (OR: 1.97, 95% CI: 0.88-3.72, p < 0.001), international normalized ratio (INR) ≥ 1.2 (OR: 3.64, 95% CI: 0.94-4.51, p < 0.001), serum creatinine > 1.0 mg/dL (OR: 2.70, 95% CI: 0.63-3.88, p < 0.001), eGFR < 60 mL/min/1.73m^2 (OR: 2.59, 95% CI: 0.63-3.01, p < 0.01), hemoglobin ≤ 10 g/dL (OR: 1.58, 95% CI: 1.37-6.23, p = 0.02), platelet ≤ 150 K/mm^3 (OR: 3.41, 95% CI: 0.56-2.70, p < 0.001), MELD score > 24 (OR: 3.90, 95% CI: 1.38-5.56, p < 0.001), Child-Pugh class C (OR: 2.50, 95% CI: 1.68-3.73, p < 0.001), ALBI (albumin-bilirubin) score grade 3 (OR: 2.29, 95% CI: 1.47-3.27, p < 0.001), and ICU admission (OR: 5.79, 95% CI: 3.61-9.29, p < 0.001) were associated with 30-day mortality (Table 5). Stepwise logistic regression analysis showed that hepatoma (aOR: 1.76, 95% CI: 1.05-2.95, p = 0.03), hepatic encephalopathy (aOR: 1.73, 95% CI: 1.05-2.87, p = 0.03), CVC use (aOR: 5.64, 3.01-10.58, p < 0.001), NI (aOR: 2.17, 95% CI: 1.36-3.47, p = 0.001), ICU admission (OR: 5.48, 95% CI: 3.15-9.54, p < 0.001), INR ≥ 1.2 (aOR: 2.57, 95% CI: 1.51-4.36, p < 0.001), eGFR< 60 mL/min/1.73m^2 (aOR: 1.99, 95% CI: 1.15-3.45, p = 0.01), platelet ≤ 150 K/mm^3 (aOR: 1.89, 95% CI: 1.08-3.29, p = 0.03), and MELD score > 24 (aOR: 2.53, 95% CI: 1.56-4.09, p < 0.001) were associated with 30-day mortality (Table 6).

Of the candidemia group patients, univariate analysis showed that CVC use (OR: 5.91, 95% CI: 3.68-15.66, p < 0.001), TPN use (OR: 12.36, 95% CI: 3.90-39.16, p < 0.001), hepatic encephalopathy (OR: 2.26, 95% CI: 0.62-2.77, p < 0.001), ascites (OR: 1.69, 95% CI: 0.33-1.52, p = 0.009), NI (OR: 2.46, 95% CI: 1.68-3.61, p < 0.001), antibiotics exposure ≥ 14 days (OR: 2.36, 95% CI: 6.27-30.97, p < 0.001), albumin ≤ 3 g/dL

Table 4

Stepwise logistic regression analysis for candidemia in patients with cirrhosis and bloodstream infection (n = 460)

Variables	Beta	aOR (95% CI)	*p*
Nosocomial infection	1.17	3.22 (1.03-10.2)	0.044
ICU admission	1.71	5.52 (2.27-13.40)	<0.001
Antibiotics exposure ≥ 14 d	2.08	8.00 (3.14-20.36)	<0.001
White cell count > 10 K/mm^3	1.03	2.79 (1.18-6.61)	0.020
MELD score > 24	1.24	3.45 (1.44-8.27)	0.005
c-statistic		0.890 (0.83-0.95)	<0.001
Hosmer-Lemeshow test		χ^2 = 5.05	0.65

aOR = adjusted odds ratio; CI, confident interval; ICU = intensive care unit; MELD = model for end-stage liver disease.

(OR: 2.06, 95% CI: 1.35-3.14, p = 0.001), total bilirubin ≥ 2 mg/dL (OR: 1.97, 95% CI: 0.88-3.72, p < 0.001), INR ≥ 1.2 (OR: 3.64, 95% CI: 0.94-4.51, p < 0.001), serum creatinine > 1.0 mg/dL (OR: 2.70, 95% CI: 0.63-3.88, p < 0.001), eGFR < 60 mL/min/1.73m^2 (OR: 2.59, 95% CI: 0.63-3.01, p < 0.01), hemoglobin ≤ 10 g/dL (OR: 1.58, 95% CI: 1.37-6.23, p = 0.02), platelet ≤ 150 K/mm^3 (OR: 3.41, 95% CI: 0.56-2.70, p < 0.001), MELD score > 24 (OR: 3.90, 95% CI: 1.38-5.56, p < 0.001), Child-Pugh class C (OR: 1.78, 95% CI: 1.19-2.68, p = 0.005), ALBI (albumin-bilirubin) score grade 3 (OR: 2.77, 95% CI: 1.38-5.56, p = 0.004), and ICU admission (OR: 5.79, 95% CI: 3.61-9.29, p < 0.001) were associated with 30-day mortality (Table 7). Stepwise logistic regression analysis showed that CVC use (aOR: 10.89, 1.14-104.06, p = 0.04) and INR ≥ 1.2 (aOR: 26.62, 95% CI: 2.37-298.88, p = 0.008) were associated with 30-day mortality.

3.4. Studies of candida infection in cirrhotic patients

Ninety-six published reports were identified initially, with 90 reports being excluded as titles or abstracts did not meet the selection criteria (82 reports), or were review articles (four reports), editorial (one report), and case reports (three reports). The remaining six studies are summarized in Table 8.[5,10,15–18] The incidence of candidemia ranged from 0.48% to 4.8% and the short-term mortality rates ranged from 29% to 47% in hospitalized cirrhotic patients. *Candida albicans* was the most common species, which was similar to our study. Acute-on-chronic liver failure, diabetes, previously gastrointestinal endoscopy and surgery, acute kidney injury, and infection on admission were among the reported risk factors for occurrence of candidemia in addition to the findings of our study. Moreover, age, severe sepsis, candida score, the length of ICU stay, early CVC removal, previously antifungal therapy, worsening of MELD score, spontaneous bacterial peritonitis, and inappropriate antibiotic therapy were additional predictors for mortality.

4. DISCUSSION

Fungal infection usually indicates a poor prognosis in immunocompromised patients including patients with cirrhosis. This study found that candidemia was present in 7.6% of the hospitalized patients with cirrhosis and BSI. We found that NI, ICU admission, antibiotics exposure ≥14 days, white cell count >10 K/mm^3, and MELD score >24 were associated with candidemia. Meanwhile, NI, ICU admission, hepatoma, hepatic encephalopathy, INR ≥1.2, platelet ≤150 K/mm^3, eGFR <60 mL/min/1.73m^2, and MELD score >24 were predictors for 30-day mortality. Six studies related to candidemia in cirrhotic patients were identified in the Pubmed database.

Fungal infection was found in 4.9% of the hospitalized patients with cirrhosis.[5] Candidemia could be present in approximately 7% to 10% of the BSI in hospitalized patients with cirrhosis.[9,18,19] Fungal infections in patients with cirrhosis are mainly caused by Candida species,[5,20] with the distribution and frequency of Candida species causing candidemia being highly dependent on the patient's underlying condition, the antifungal agents used and hospital-related factors.[21] *C. albicans* was the dominant Candida species in our study, followed by *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, and *C. krusei*. *C. albicans* is the most common species present in candidemia, but its frequency is decreasing.[21] In recent years, the frequency of *C. glabrata* and *C. krusei* have been stable while *C. parapsilosis* and

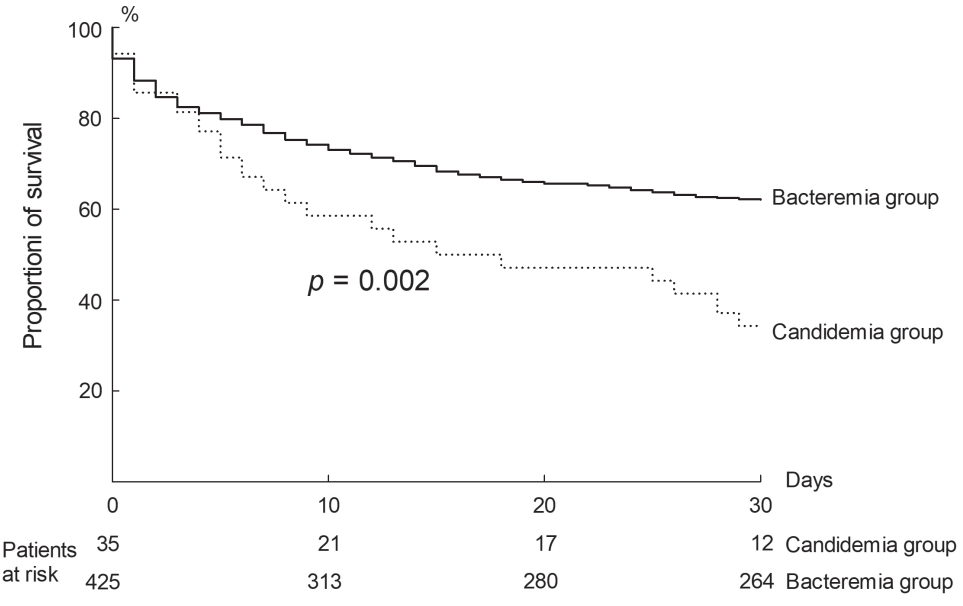

Fig. 2 Thirty-day survival of cirrhotic patients with candidemia and noncandidemia bloodstream infection. The patients with candidemia had significantly higher mortality rate compared with the patients with non-candidemia bloodstream infection.

Table 5

Univariate logistic regression analysis for 30-day mortality in patients with cirrhosis and bloodstream infection (n = 460)

Variables	Beta	OR (95% CI)	*p*
Age	−0.002	0.99 (0.99-1.01)	0.18
Male gender	−0.10	0.90 (0.61-1.34)	0.61
Comorbidity			
Hypertension	0.01	1.01 (0.70-1.48)	0.95
Diabetes mellitus	−0.32	0.73 (0.48-1.11)	0.14
Hyperlipidemia	−0.25	0.78 (0.24-1.48)	0.27
Congestive heart failure	−0.35	0.71 (0.15-1.75)	0.22
HCC	0.37	1.45 (0.35-1.77)	0.08
Hepatitis B	0.28	1.32 (0.74-3.36)	0.16
Hepatitis C	0.45	1.57 (0.25-2.13)	0.09
CVC use	1.78	5.91 (3.68-15.66)	<0.001
TPN use	2.51	12.36 (3.90-39.16)	<0.001
Hepatic encephalopathy	0.82	2.26 (0.62-2.77)	<0.001
Ascites	0.52	1.69 (0.33-1.52)	0.009
Nosocomial infection	0.90	2.46 (1.68-3.61)	<0.001
Antibiotics exposure ≥ 14 d	0.86	2.36 (6.27-30.97)	<0.001
Laboratory data			
Albumin ≤ 3 mg/dL	0.72	2.06 (1.35-3.14)	0.001
Total bilirubin ≥ 2 mg/dL	0.68	1.97 (0.88-3.72)	<0.001
INR ≥ 1.2	1.29	3.64 (0.94-4.51)	<0.001
Creatinine > 1.0 mg/dL	0.99	2.70 (0.63-3.88)	<0.001
eGFR < 60 mL/min/1.73m^2	0.95	2.59 (0.63-3.01)	<0.01
Hemoglobin ≤ 10 g/dL	0.46	1.58 (1.37-6.23)	0.02
Platelet ≤ 150 K/mm^3	1.23	3.41 (0.56-2.70)	<0.001
White cell count > 10 K/mm^3	0.07	1.07 (1.18-5.03)	0.73
MELD score > 24	1.36	3.90 (1.38-5.56)	<0.001
Child-Pugh class C	0.92	2.50 (1.68-3.73)	<0.001
ALBI score grade 3	0.78	2.29 (1.47-3.27)	<0.001
ICU admission	1.76	5.79 (3.61-9.29)	<0.001

ALBI = albumin-bilirubin; CI = confident interval; CVC = central venous catheter; eGFR = estimated glomerular filtration rate; HCC = hepatocellular carcinoma; INR = international normalized ratio; MELD = model for end-stage liver disease; OR, odds ratio; TPN = total parenteral nutrition.

C. tropicalis are increasing. In a case-control study of cirrhotic patients with candidemia, *C. albicans* accounted for 64% of the cases, followed by *C. parasilosis* (14%) and *C. glabrata* (9%).[10] In another study, *C. albicans* (54.%) was the most common species, while *C. parasilosis* (14.1%) and *C. glabrata* (14.5%) had similar proportions.[16]

Candidemia may arise both endogenously and exogenously in patients with liver cirrhosis. However, previous antibiotics use is considered as the most important factor associated with candidemia in patients with cirrhosis.[7,10,12,20] Emergence of fungal dysbiosis in gut microbiota could be the cause of fungal infection development in cirrhotic patients receiving antibiotics treatment.[22] The presence of CVC, especially if used for TPN, is the second common factor associated with candidemia in patients with cirrhosis.[10,18,20] The other predictors for candidemia include ICU admission,[5] longer hospital stay,[18] advanced cirrhosis or acute-on-chronic liver failure,[7,10] diabetes,[5] invasive procedures,[10] acute kidney injury,[5] and surgery.[18] It was noteworthy that white cell count >10 K/mm^3 was found to be a predictor for candidemia in our study. The clinical manifestations of candidemia could vary from mild fever to severe sepsis that resembles bacterial infection. Neutropenia was less common than expected in patients with candidemia.[23] Actually, leukocytosis could be identified in patients with candidemia.[24]

Presumptive antifungal therapy based on symptoms or biomarkers could reduce mortality in patients with candidemia.[25] Thirty candidemia patients received antifungal therapy and 68% were successfully treated while five patients were not treated because the blood culture grew out fungus after the patients expired. In a study of cirrhotic patients with candidemia and intra-abdominal candidiasis, 83.8% of the patients received adequate antifungal therapy.[16] However, as low as 47% of fungal infections in cirrhotic patients are typically diagnosed and treated with antifungal agents.[6] Echinocandins are usually recommended as the first-line treatment in patients with severe

Table 6

Stepwise logistic regression analysis for 30-day mortality in patients with cirrhosis and bloodstream infection (n = 460)

Variables	Beta	aOR (95% CI)	*p*
HCC	0.57	1.76 (1.05-2.95)	0.03
Hepatic encephalopathy	0.55	1.73 (1.05-2.87)	0.03
Nosocomial infection	0.24	2.17 (1.36-3.47)	0.001
ICU admission	1.70	5.48 (3.15-9.54)	<0.001
INR ≥ 1.2	0.94	2.57 (1.51-4.36)	<0.001
eGFR< 60 mL/min/1.73m^2	0.69	1.99 (1.15-3.45)	0.01
Platelet ≤ 150 K/mm^3	0.64	1.89 (1.08-3.29)	0.03
MELD score > 24	0.93	2.53 (1.56-4.09)	<0.001
c-statistic		0.82 (0.78-0.86)	<0.001
Hosmer-Lemeshow test		χ^2 = 12.31	0.14

aOR = adjusted odds ratio; CI = confident interval; eGFR = estimated glomerular filtration rate; HCC = hepatocellular carcinoma; ICU = intensive care unit; INR = international normalized ratio; MELD = model for end-stage liver disease.

Table 7

Univariate logistic regression analysis for 30-day mortality in patients with cirrhosis and candidemia (n = 35)

Variables	Beta	OR (95% CI)	*p*
Age	−0.04	0.96 (0.91-1.01)	0.09
Male gender	−0.10	0.90 (0.61-1.34)	0.61
Comorbidity			
Hypertension	0.01	1.01 (0.70-1.48)	0.95
Diabetes mellitus	−0.32	0.73 (0.48-1.11)	0.14
Hyperlipidemia	−0.25	0.78 (0.24-1.48)	0.27
Congestive heart failure	−0.35	0.71 (0.15-1.75)	0.21
HCC	0.37	1.45 (0.35-1.77)	0.08
Hepatitis B	0.28	1.32 (0.74-3.36)	0.16
Hepatitis C	0.45	1.57 (0.25-2.13)	0.09
CVC use	1.78	5.91 (3.68-15.66)	<0.001
TPN use	2.51	12.36 (3.90-39.16)	<0.001
Hepatic encephalopathy	0.82	2.26 (0.62-2.77)	<0.001
Ascites	0.52	1.69 (0.33-1.52)	0.009
Nosocomial infection	0.90	2.46 (1.68-3.61)	<0.001
Antibiotics exposure ≥ 14 d	0.86	2.36 (6.27-30.97)	<0.001
Laboratory data			
Albumin ≤ 3 mg/dL	0.72	2.06 (1.35-3.14)	0.001
Total bilirubin ≥ 2 mg/dL	0.68	1.97 (0.88-3.72)	<0.001
INR ≥ 1.2	1.29	3.64 (0.94-4.51)	<0.001
Creatinine > 1.0 mg/dL	0.99	2.70 (0.63-3.88)	<0.001
eGFR < 60 mL/min/1.73m^2	0.95	2.59 (0.63-3.01)	<0.001
Hemoglobin ≤ 10 g/dL	0.46	1.58 (1.37-6.23)	0.012
Platelet ≤ 150 K/mm^3	1.23	3.41 (0.56-2.70)	<0.001
White cell count > 10 K/mm^3	0.07	1.07 (1.18-5.03)	0.73
MELD score > 24	1.36	3.90 (1.38-5.56)	<0.001
Child-Pugh class C	0.58	1.78 (1.19-2.68)	0.005
ALBI score grade 3	1.02	2.77 (1.38-5.56)	0.004
ICU admission	1.76	5.79 (3.61-9.29)	<0.001

ALBI = albumin-bilirubin; CI = confident interval; CVC = central venous catheter; eGFR = estimated glomerular filtration rate; HCC = hepatocellular carcinoma; ICU = intensive care unit; INR = international normalized ratio; MELD = model for end-stage liver disease; OR, odds ratio; TPN = total parenteral nutrition.

Table 8

Summary of studies of candida infection in patients with cirrhosis

Study	Country	Population	Microbiology	Result
Bartoletti 2021[10]	Italy	450 in cirrhotic patients (90 with candidemia, 180 with bacteremia, and 180 negative culture)	*C. albicans* (64%) *C. parapsilosis* (14%) *C. glabrata* (9%) *C. tropicalis* (4%) Other spp. (8%)	• Acute-on-chronic liver failure within 30 d, previously gastrointestinal endoscopy, previously antibiotic treatment for at least 7 d, presence of a central venous catheter, TPN, and length of in-hospital >15 d were factors associated with candidemia.
Schroeder 2020[15]	Germany	391 candidemia patients (incidence 4.8/1000 in ICU admissions)	*C. albicans* (61%) *C. glabrata* (19.4%) *C. parapsilosis* (6.6%) *C. tropicalis* (5.8%) *C. dubliniensis* (3.3%) *C. krusei* (1.7%) Other spp. (2%)	• 28 d mortality rate was 47%; 180 d mortality rate was 60%. • Age, cirrhosis, septic shock, the Sepsis-related Organ Failure Assessment score, Candida score, and the length of ICU stay were risk factors for death at 180 d.
Bajaj 2018[5]	USA	2743 cirrhotic patients (134 fungal infections, 4.8%)	*C. albicans* (43.2%) *C. parapsilosis* (6.2%) *C. glabrata* (6.2%)	• Diabetes, AKI, ICU admission, and infection on admission were predictors for fungal infection development.
Bassetti 2017[16]	Europe (Italy, Spain Ireland, Belgium Greece)	241 candida infectious episodes in cirrhotic patients (169 candidemia episodes, 72 intra-abdominal candidiasis)	*C. albicans* (54.4%) *C. glabrata* (14.5%) *C. parapsilosis* (14.1%)	• 30 d mortality was 35.3%. • Candidemia and septic shock were factors associated with 30 d mortality. • Adequate antifungal treatment had survival benefits.
González-Lara 2017[17]	Mexico	149 candida BSI	*C. albicans* (40%) *C. tropicalis* (23%) *C. glabrata* (20%) *C. parapsilosis* (10%) *C. guilliermondi* (2%) *C. krusei* (1.3%)	• 30 d mortality was 38%. • Severe sepsis, cirrhosis, early central venous catheter removal, and previously antifungal therapy were associated with 30 d mortality.
Bartoletti 2014[18]	Italy	8874 cirrhotic patients (162 BSI, 1.8%; 16 candidemia, 0.18%)	*C. albicans* (87.5%) *C. parapsilosis* (6.2%) *C. glabrata* (6.2%)	• Overall 30 d mortality for BSI was 29%. • Worsening of MELD score, spontaneous bacterial peritonitis, sepsis grading, and inappropriate antibiotic therapy were factors associated with 30 d mortality. • Candida BSI was more common in cirrhotic patients with a hospital stay of more than 6 d, hospital-acquired BSI, prior surgery, central venous catheter, neutrophilia, or prior piperacillin-tazobactam or fluoroquinolone antibiotic therapy. • Candida BSI has the strongest association with inappropriate empirical antibiotics therapy

AKI = acute kidney injury; BSI = bloodstream infection; *C. albicans* = *Candida albicans*; *C. glabrata* = *Candida glabrata; C. guilliermondi* = *Candida guilliermondi*; *C. krusei* = *Candida krusei; C. parapsilosis* = *Candida parapsilosis; C. tropicalis* = *Candida tropicalis;* ICU = intensive care unit; MELD = model for end-stage liver disease; TPN = total parenteral nutrition.

fungal infection.[26] More importantly, the proportion of Candida species may determine the susceptibility to antifungal agents because *C. glabrata* has diminished susceptibility to azoles, and echinocandins are less effective for *C. parapsilosis*.[21]

The 30-day mortality rate was 65.7% in the candidemia group in our study. In addition to candidemia itself, severe infection in patients with cirrhosis might induce a rapid deterioration of liver function, acute-on-chronic liver failure, and even death.[27,28] The 30-day mortality of cirrhotic patients with candidemia has ranged between 35.3% to 64%.[5,10,16] The highly variable mortality, as well as the incidence of candidemia, could be due to the retrospective nature and difference of locations between the studies. The factors associated with mortality in patients with cirrhosis and candidemia have included MELD score, ICU or medical wards admission, grade 2 or grade 3 acute-on-chronic liver failure and septic shock.[10,16] Despite the high mortality rate, the candidemia group only had borderline significant association with 30-day mortality in a multivariate analysis compared with the bacteremia group in our study. This result is consistent with a previous study of patients with cirrhosis and BSI.[10] It is possible that patients with cirrhosis and BSI have high mortality and the factors related to the liver reserve might play a more important role than candidemia.

Only a few retrospective cohort studies related to candida infections in cirrhotic patients were identified in our literature search. These studies were conducted in general wards or ICUs with different study populations and the status of fungal infections included nonsystemic infection, intra-abdominal candidiasis, and candidemia. However, low incidence of candidemia, high mortality rates, and common predictors for occurrence of candidemia and mortality were validated despite the study heterogeneity. Future well-designed, randomized controlled trials are needed for the diagnosis and management of candidemia in patients with cirrhosis.

The current study has some limitations. First, it was a single-center, retrospective cohort study and the results might not be representative of other institutions because of the differences between etiology of cirrhosis and the susceptibility of candida and bacteria between regions. Second, this study was limited in obtaining the susceptibility of the anti-fungal agent in isolated candida species, so further analysis is needed for more discussion. The early symptoms of fungal BSI are usually nonspecific and the low culture-positive rate and the incidence of candidemia could be underestimated.[29]

In this cohort study of the hospitalized patients with cirrhosis and BSI, we found a low incidence of candidemia with higher

mortality compared with the group of bacteremia patients. Identification of the predictors for candidemia could be helpful for early detection of candidemia and administration of antifungal agents to improve the outcome of cirrhotic patients with candidemia.

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