Clinical characteristics, risk factors, and outcomes of Candida albicans bloodstream and lower respiratory tract infections

Yizhi Wang*

Institute of Cardiovascular Diseases, Hubei Province Key Laboratory of Occupational Hazard Identification and Control, School of Medicine, Wuhan University of Science and Technology, Wuhan 430065, Hubei, China

Abstract: The purpose of this study was to investigate the clinical characteristics, risk factors and prognosis of patients with Candida albicans blood flow and lower respiratory tract infection

Method: The data of 164 patients with suspected Candida albicans infection in a regional tertiary teaching hospital in China from January 2020 to December 2022 were analyzed retrospectively. We collected electronic recording data from patients with single Candida albicans bloodstream infection and patients with single Candida albicans lower respiratory tract infection. Mann-Whitney U test was used for retrospective study. Logistic regression analysis and comparison of prognostic risk factors between patients with single Candida albicans bloodstream infection and single Candida albicans lower respiratory tract infection.

Results: among the 164 patients suspected of Candida albicans infection, 81 cases were diagnosed as single Candida albicans bloodstream infection (49.4%, 81/164). The average age of the patients was 57.4 years old, 51 cases (63.0%) were male, and the 30-day mortality was 18.5%. Multivariate regression analysis showed that hematologic malignancy [(OR),1.221; 95%(CI), 1.048~2.820, p=0.043)] was an independent predictor of 30-day mortality in patients with single Candida albicans bloodstream infection, length of stay [(OR), 0.924; 95% (CI), 0.868 ~ 0.983, p=0.012] and time of hormone use [(OR), 0.927]. 95% (CI), 0.870-0.988, p=0.019] were protective factors for patients with single Candida albicans bloodstream infection. There were 84 cases of lower respiratory tract infection caused by Candida albicans (51.2%, 84/164). The average age of the patients was 69.8 years old, and 70 cases (83.3%) were male. Three patients were randomly selected from 84 patients and 81 patients were analyzed. The 30-day mortality rate was 13.6%. Multivariate regression analysis showed that cerebrovascular accident [(OR), 1.072; 95%(CI),1.015~1.150, p=0.012] was an independent predictor of 30-day mortality in patients with Candida albicans lower respiratory tract infection.

Conclusion: The proportion of lower respiratory tract infection in patients with Candida albicans infection is higher, and the basic diseases of patients with Candida albicans infection are mainly cerebrovascular accidents. There was no significant difference in mortality between patients with bloodstream infection and patients with lower respiratory tract infection, but patients with invasive operations such as CVC had a higher risk of bloodstream infection with single Candida albicans than patients with lower respiratory tract infection with single Candida albicans, which deserves further attention from clinicians. The analysis of this study shows that we should attach great importance to and guard against Candida infection in inpatients, and timely intervention treatment should be carried out when Candida infection is considered and Candida colonization is excluded. Correct identification of Candida albicans infection is particularly important to control infection and improve the condition. The monitoring of flora should be strengthened in key departments. Standardized intervention treatment after timely detection and diagnosis of Candida infection can effectively improve the prognosis of patients. The analysis of this study shows that we should attach great importance to and guard against Candida infection in inpatients, and timely intervention treatment should be carried out when Candida infection is considered and Candida colonization is excluded. Correct identification of Candida albicans infection is particularly important to control infection and improve the condition. The monitoring of flora should be strengthened in key departments. Standardized intervention treatment after timely detection and diagnosis of Candida infection can effectively improve the prognosis of patients.

1. Introduction

Fungal infection (Fungal infection) has become a serious cause of human infection, especially in hospitalized patients. There are more than 50 kinds of common pathogenic fungi in clinic.[1] In recent years, the prevalence of serious diseases caused by fungal infection has soared. Scholars at home and abroad generally believe that the increase in the incidence of fungal diseases is

*E-mail: zhiyw111@163.com

related to many factors, such as the increase in the number of immune impaired hosts (including cancer patients, organ transplant recipients, people living with HIV and the growing elderly population) and the increase in some medical procedures and the widespread use of drugs. Examples include broad-spectrum antibiotics, the use of immunosuppressants, and invasive surgical procedures[2, 3]. The common pathogenic fungus in China is Candida, and the most common pathogen in fungal infection in patients with severe immune impairment and invasive clinical operation is Candida albicans, especially Candida albicans (C.albicans). Candida albicans is the main cause of invasive candidiasis[4, 5]. Although medical institutions have carried out intervention treatment against Candida albicans infection, the crude death rate of infected patients is as high as 40%[6]. In many healthy individuals, Candida albicans can exist in the host's oral cavity, vagina or gastrointestinal tract. However, in immunodeficient or immunosuppressive or impaired patients, the fungus can spread to the blood and even proliferate in internal organs, resulting in life-threatening systemic infections[7].

Candida is an important pathogen of nosocomial bloodstream infection, and its incidence is on the rise in the past decade[7]. The diagnosis and treatment of Candida bloodstream infection places a huge burden on the health care system. A prospective study in 2019 reported that Candida infection in the United States resulted in an average increase of 34 days in hospital stay for patients diagnosed with Candida bloodstream infection at an additional cost of $34123 per case[8].It is reported that the mortality rate of Candida bloodstream infection is as high as 60%, 70%, in some populations[9]. A five-year study conducted in the western region (1998-2002) showed that 2.8 per cent of all culture-positive bloodstream infections in secondary hospitals were associated with Candida albicans, 46 per cent of which were attributed to Candida albicans[10]. This is supported by two other studies in central Colorado, which found that Candida albicans accounted for 38.7% and 50.7% of Candida albicans infections, respectively. A recent study conducted by Al-Dorzi et al in the intensive care unit of Saudi Arabia Central Hospital found that among the 174 fungal bloodstream infections from 2012 to 2016, the most common pathogen was Candida albicans, with mortality rates of 61.3% and 54.9% for Candida albicans and NAC, respectively. Most deaths occurred within 28 days after positive culture was detected, and the hospitalization time and intensive care time of the two groups were similar[11].

Candida is usually isolated from lower respiratory secretions such as endotracheal inhalation or bronchoalveolar lavage fluid (BAL) in critically ill intubated and mechanically ventilated patients. Invasive pulmonary Candida infection is considered to be very rare or even non-existent in autopsy studies. However, Roux et al found that the colonization of Candida in the lower respiratory tract can induce Th1-Th17 immune response in rats, which can promote the release of cytokines and cause pneumonia, and the timely use of antifungal drugs can prevent the occurrence of the above pathological changes[12]. Wiliamson and other studies have confirmed that Candida colonization in the lower respiratory tract can promote systemic inflammatory response syndrome in patients with ventilator-associated pneumonia (Ventilator-associated pneumonia, VAP)Zhang and others have studied that the isolation rate of multiple drug-resistant bacteria (Multiple Drug Resistant, MDR) and the incidence of VAP in mechanically ventilated patients with Candida albicans in deep sputum and antifungal drugs can be reduced, and the time of mechanical ventilation and hospitalization in intensive care unit as well as the total hospitalization time of patients can be shortened.

Candida albicans infection in patients with high mortality, drug resistance is increasing, clinical treatment is very difficult. Therefore, to be familiar with and master the clinical characteristics and prognostic factors of patients with Candida albicans bloodstream infection and Candida albicans pneumonia has important guiding significance and value for reducing the morbidity and mortality of Candida albicans infection. In this study, a retrospective analysis was used to collect the clinical data of patients suspected of Candida albicans bloodstream infection and Candida albicans lower respiratory tract infection in a regional tertiary teaching hospital in China from January 2020 to December 2022. Analyze the characteristics of Candida albicans infection and explore related prognostic factors. The aim is to provide clinicians with early diagnosis and early treatment of Candida infection and to provide reference for the treatment of Candida infection so as to reduce the mortality of patients with Candida infection.

2. Objects and methods

2.1. Object

A total of 164 patients with Candida albicans infection in the microbiology laboratory of a regional tertiary teaching hospital in China from January 2020 to December 2022 were selected. 81 patients were diagnosed as single Candida albicans bloodstream infection and 81 patients with Candida albicans lower respiratory tract infection, including 97 patients with Candida albicans bloodstream infection and 16 patients with Candida albicans lower respiratory tract infection.

2.2. Inclusion and exclusion criteria

Selection criteria: (1) not less than 18 years old; (2) in accordance with the diagnostic criteria of Candida bloodstream infection and Candida lower respiratory tract infection: according to the diagnostic criteria of Chinese Adult Candida diagnosis and treatment expert consensus of Chinese Medical Association in 2020, Candida was diagnosed according to European Cancer Research and treatment Organization/invasive fungal infection Cooperation Group. Candida albicans bloodstream infection confirmed that the patient had the symptoms or signs of Candida albicans bloodstream infection, and one or more blood cultures were positive for Candida albicans. Lower respiratory tract infection of Candida albicans was confirmed as follows: 1) qualified sputum or BALF specimens showed positive Pseudohypha or hyphae under microscope, and Candida albicans grew for more than 3

times; the quality of samples was examined and evaluated by Bartlett (Q) grading system, 10 low power visual fields under microscope (<10 neutrophils/LPF=0; 10-20 neutrophils/LPF=+1;> neutrophils/LPF=+2; mucus =+1). Leukocytes, mucus and squamous epithelial cells were found in 10-25 squamous epithelial cells/LPF=-1; > 25 squamous epithelial cells/LPF=-2. Score <1: sputum samples were seriously contaminated; score ≥ 1: "uncontaminated" sputum specimens with inflammation, and deep trachea secretions were considered uncontaminated. When the uncontaminated sputum samples and all deep tracheal secretions were cultured as Candida albicans, the infection of the patient was considered to be related to Candida albicans lower respiratory tract infection. 2) the infected patients had symptoms of pneumonia and new focal or diffuse bronchopneumonia on chest X-ray or CT. 3) excluding pneumonia caused by other pathogens. 4) fungal G and GM tests were positive for 2 consecutive times.

Exclusion criteria: (1) age < 18 years old; (2) sputum culture or BALF culture of Candida albicans but no corresponding infection symptoms, normal laboratory examination, no progress without intervention treatment, considering Candida albicans colonization; (3) sputum culture with other pathogens infection; (4) long-term hospitalization; (5) incomplete data or automatic discharge or death of unknown causes

3. Method

A retrospective study was conducted to consult the medical records to screen and collect the clinical data of patients with Candida albicans bloodstream infection and Candida albicans lower respiratory tract infection, and to eliminate the cases with incomplete data. including: general conditions: sex, age, hospitalization time (days), blood routine, biochemistry, Candida albicans positive time for the first time during hospitalization. Basic diseases: respiratory diseases such as chronic obstructive pulmonary disease, coronary heart disease, hypertension, diabetes, cerebrovascular accidents (cerebral hemorrhage and infarction, etc.), malignant tumors, hematological diseases, etc. Invasive procedures: mechanical ventilation, endotracheal intubation, tracheotomy, indwelling gastric catheter, central venous catheterization, etc. Use of antibiotics before and after infection: combination of β-lactam and enzyme inhibitors, carbapenem, aminoglycosides, fluoroquinolones and antibiotics. The same Candida albicans was cultured in the same patient at different times, and only one case of infection was counted, and the first isolation and culture event was analyzed (Fig.1).

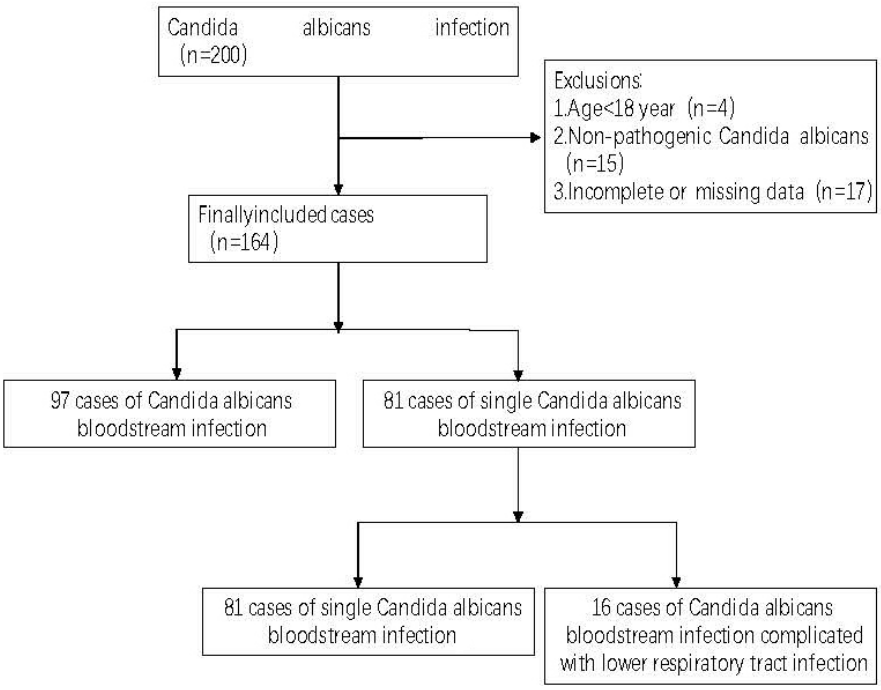


Figure.1 Flowchart of study participant enrollment

3.1. Statistical analysis

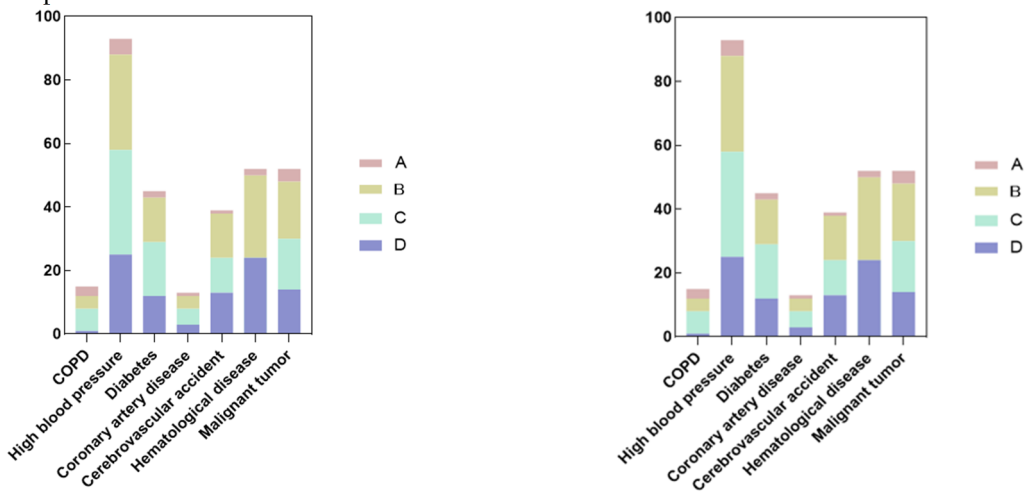
The data were analyzed by SPSS 25.0 and GraphPad Prism 9.0.0 software. The normal distribution data were expressed as mean ±standard deviation, and the non-normal distribution data were expressed in the range of median and quartile. Univariate analysis: the measurement data were analyzed by t-test if the homogeneity of variance was used, otherwise Satterthwaite approximate t-test was used, and the counting data were analyzed by X^2 test. Multivariate analysis: the statistically significant variables in univariate analysis were included in Logistic multivariate regression analysis, and the OR value and 95%CI were calculated.

3.2. Result

During the period of our study, 81 patients were selected from 164 patients with suspected Candida albicans

bloodstream infection and 81 patients with Candida albicans lower respiratory tract infection. The average age of patients with single Candida albicans bloodstream infection was 57.4 years old, 51 males (63.0%), 54 patients (66.7%) had underlying diseases, most of them were malignant tumors of the blood system (29.6%) and cardiovascular diseases (34.6%). The average age of patients with single Candida albicans lower respiratory tract infection was 69.8 years old, 70 males (86.4%), 69 patients (82.1%) had underlying diseases, mainly chronic respiratory diseases (45.3%) and cerebrovascular diseases (13.1%). The detailed data is shown in figure 2. In addition, the most common invasive procedure for single Candida albicans bloodstream infection was central venous catheterization in 66 cases (81.5%), followed by indwelling catheter in 49 cases (60.5%), indwelling gastric tube in 44 cases (54.3%), and mechanical ventilation in 31 cases (38.3%). The most common invasive operation of Candida albicans lower respiratory tract infection was indwelling gastric tube in 52 cases (61.9%), indwelling catheter in 50 cases (59.5%), central venous catheter in 49 cases (58.3%), and mechanical ventilation in 36 cases (42.9%). Except for chronic respiratory diseases COPD and hematological malignancies there was no statistically significant difference in potential complications between patients with single Candida albicans bloodstream infection and patients with single Candida albicans lower respiratory tract infection. In addition there was no statistically significant difference in invasive procedures between patients with single Candida albicans bloodstream infection and patients with Candida albicans lower respiratory tract infection except CVC and tracheotomy. The demographic and clinical features of the patients are summarized in Table 1. In order to compare the correlation between the variables with significant differences in univariate analysis between the two groups, the correlation analysis and visual analysis were carried out. The detailed data is shown in figure 3.

The 30-day mortality rate of 164 patients was 15.9% (26/164). The 30-day mortality rates of patients with single Candida albicans bloodstream infection and patients with single Candida albicans lower respiratory tract infection were 18.5% (15/81) and 13.6% (11/81), respectively. Univariate predictors of adverse outcomes caused by single Candida albicans bloodstream infection are shown in Table 2. The results of multivariate analysis showed that hematologic malignancy [(OR),1.221; 95%(CI), 1.048~2.820, p=0.043)] was an independent predictor of 30-day mortality in patients with single Candida albicans bloodstream infection, length of stay [(OR), 0.924; 95% (CI), 0.868 ~ 0.983, p=0.012], hormone use time[(OR), 0.927]. 95% (CI), 0.870-0.988, p= 0.019] are protective factors for patients with single Candida albicans bloodstream infection. Univariate predictors of adverse outcomes caused by Candida albicans lower respiratory tract infection are shown in Table 3. Multivariate analysis showed that cerebrovascular accident [(OR), 1.072; 95%(CI),1.015~1.150, p=0.012] was an independent predictor of 30-day mortality in patients with Candida albicans lower respiratory tract infection. The detailed data is shown in figure 4.



(a) (b)

A: Blood flow infection of Candida albicans complicated with lower respiratory tract infection of Candida albicans
B: Bloodstream infection of Candida albicans
C: Single Candida albicans lower respiratory tract infection
D:S ingle Candida albicans bloodstream infection

Fig 2. a: distribution of underlying diseases in patients with Candida albicans infection; b: distribution of invasive procedures in patients with Candida albicans infection

Table 1. Baseline characteristics of patients with single Candida albicans bloodstream infection and lower respiratory tract infection

	Bloodstream infection	Low respiratory tract infection	P
Age	57.38±17.692	69.83±10.373	<0.001
Hospitalization days	27 (13, 35)	24 (15.5, 30)	0.313
COPD	1 (1.2)	7 (8.6)	0.03
High blood pressure	25 (30.9)	33 (40.7)	0.191

Diabetes	12 (14.8)	17 (21)	0.307
Coronary artery disease	3 (3.7)	4 (4.9)	0.7
Cerebrovascular accident	13 (16)	11 (13.6)	0.659
Hematological disease	24 (29.6)	0 (0)	<0.001
Malignant tumor	14 (17.3)	16 (19.8)	0.687
WBC (10^9/L)	6.44 (3.085, 13.045)	10.81 (7.84, 14.365)	<0.001
NE (10^9/L)	5.77 (2.45, 12.12)	9.45 (6.41, 12.855)	0.001
NE%	84.3 (62.9, 93.1)	85.9 (81.75, 90.15)	0.317
PLT (10^9/L)	101.5 (37.75, 219.25)	168 (105, 235.5)	0.002
RBC (10^{12}/L)	2.88±0.801	3.61 (2.925, 4.005)	<0.001
HGB (g/L)	85.16±23.285	105.86±22.713	<0.001
TBIL (umol/L)	13.9 (10.15, 27.65)	13.9 (8.765, 21.35)	0.474
ALT (U/L)	23 (11.95, 41.8)	14.8 (12.2, 31.75)	0.475
AST (U/L)	26.3 (16.55, 46.65)	28.2 (21.3, 52.7)	0.199
ALB (g/L)	32.21±6.480	31.98±5.661	0.806
Cr (umol/L)	62.3 (47.1, 135.2)	66.1 (53.45, 110.5)	0.437
Invasive mechanical ventilation	31 (38.3)	34 (42)	0.632
Endotracheal intubation	23 (28.4)	33 (40.7)	0.1
Endotracheal intubation time	0 (0, 2.5)	0 (0, 9)	0.077
Tracheotomy	16 (19.8)	5 (6.2)	0.01
Tracheotomy time	0 (0, 0)	0 (0, 0)	0.032
Indwelling gastric tube	44 (54.3)	50 (61.7)	0.341
Indwelling time ofgastric tube	4 (0, 15.5)	8 (0, 21)	0.224
Indwelling catheter	49 (60.5)	48 (59.3)	0.873
Indwelling catheter time	6 (0, 17.5)	7 (0, 20)	0.876
Central venous catheter	66 (81.5)	47 (58)	0.001
Indwelling time of central venous catheter	13 (2, 17)	7 (0, 19)	0.003
Operation	41 (51.2)	28 (34.6)	0.33
β-lactams and enzyme Inhibitors	36 (44.4)	40 (49.4)	0.53
Carbapenem	49 (60.5)	32 (39.5)	0.008
Hormone	0 (0, 0)	29 (35.8)	0.238
Hormone use time	0 (0, 1.5)	0 (0, 8.5)	0.054

Correlation analysis: In order to compare the correlation between the variables with significant differences in univariate analysis between the two groups, the correlation analysis between variables was carried out and the results were visualized. Fig.3.

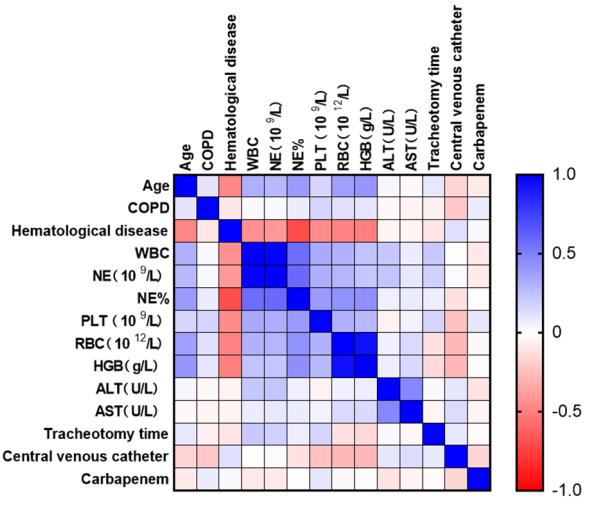


Figure.3 Correlation analysis between bloodstream and lower respiratory tract infection of Candida albicans

Table 2. prognostic analysis of patients with single Candida albicans bloodstream infection

	Death group	Survival group	P
Age	60 (45, 73)	59(45.5,72.25)	0.827
Gender (male)	8 (53.3)	42(63.6)	0.461
Hospitalization days	15 (5, 24)	28(18,38)	0.001
COPD	0	1(1.5)	0.634
High blood pressure	4 (26.7)	21(31.8)	0.698

Diabetes	3 (20)	9(13.6)	0.534
Coronary artery disease	0	3(4.5)	0.453
Cerebrovascular accident	2 (13.3)	11(16.7)	0.752
Hematological disease	5 (33.3)	19(28.8)	0.025
Malignant tumor	6 (40)	8(12.1)	0.729
WBC (109/L)	6.01(3.24,11.24)	6.52(1.4,13.72)	0.576
NE (109/L)	5.5(3.22,10.45)	5.77(1.19,12.62)	0.852
NE%	88.35(69.65,92.13)	84(57.9,93.65)	0.572
PLT (109/L)	76(48.75,196.25)	114(36.5,231.5)	0.293
RBC (1012/L)	2.671±0.35	2.92±0.814	0.278
HGB (g/L)	80.2±22.691	86.29±23.44	0.364
TBIL (umol/L)	17.9(12.6,34.2)	13.6(9.45,25.35)	0.162
ALT (U/L)	23(10.4,42.4)	22.5(12.03,41.7)	0.766
AST (U/L)	36(19.5,76.9)	25.45(16.35,39.725)	0.160
ALB (g/L)	30.2(24.9,35)	32.65±6.606	0.199
Cr (umol/L)	162.9(36.9,199.4)	61.3(48.025,100.5)	0.296
Invasive mechanical ventilation	7 (46.7)	24(36.4)	0.461
Endotracheal intubation	7 (46.7)	16(24.2)	0.084
Endotracheal intubation time	0(0, 7)	0(0.0.25)	0.123
Tracheotomy	3 (20)	13 (19.7)	0.979
Tracheotomy time	0 (0, 0)	0 (0, 0)	0.279
Indwelling gastric tube	12 (80)	32 (48.5)	0.028
Indwelling time of gastric tube	6.73±7.648	0(0,18)	0.923
Indwelling catheter	13 (86.7)	36 (54.5)	0.022
Indwelling catheter time	10.27±9.867	5.5(0,16.75)	0.487
Central venous catheter	14 (93.3)	52 (78.8)	0.193
Indwelling time of central venous catheter	12.67±11.568	14(2,28)	0.475
Operation	8 (53.3)	33 (50.8)	0.859
β-lactams and enzyme Inhibitors	5 (33.3)	31(47)	0.340
Carbapenem	11 (73.3)	38(57.6)	0.263
Hormone	6 (40)	16 (24.2)	0.218
Hormone use time	1.5 (0, 2)	0.5(0.0.25)	0.019

Table 3. Prognostic Analysis of Patients with Single Candida albicans Lower Respiratory Tract Infection

	Death group	Survival group	P
Age	74(65,81)	77 (66, 76)	0.266
Gender (male)	7 (63.6)	61(87.1)	0.149
Hospitalization days	17(11,30)	24.5 (16, 30.5)	0.214
COPD	0	7(10)	0.275
High blood pressure	4 (36.4)	29(41.4)	0.752
Diabetes	4 (36.4)	13(18.6)	0.181
Coronary artery disease	0	4(5.7)	0.419
Cerebrovascular accident	3 (27.3)	8(11.4)	0.031
Hematological disease	0	0	0.99
Malignant tumor	0	16(22.9)	0.079
WBC (109/L)	9.77(7.91,20.55)	10.88 (7.75, 14.06)	0.715
NE (109/L)	7.37(6.45,18.58)	9.52 (6.39, 12.33)	0.699
NE%	85.8(82.2,93.1)	86.4 (80.98, 89.93)	0.499
PLT (109/L)	110(99,229)	170.5 (105.5, 238.75)	0.341
RBC (1012/L)	3.63±0.522	3.56±0.917	0.829
HGB (g/L)	108.64±17.625	105.43±23.488	0.666
TBIL (umol/L)	16.6(14.5,23.9)	13.5 (8.675, 19.55)	0.087
ALT (U/L)	12,2(12.2,16)	17.1 (12.2, 36.6)	0.153
AST (U/L)	33.6(23.5,52.8)	28.15 (20.85, 54.4)	0.82
ALB (g/L)	32.2(28.6,34.7)	32.04±5.743	0.802
Cr (umol/L)	95 (52.5, 108)	66.1 (53.575, 119.85)	0.923
Invasive mechanical ventilation	7 (63.6)	27(38.6)	0.12
Endotracheal intubation	7 (63.6)	26(37.1)	0.099
Endotracheal intubation time	7.64±8.286	0(0,9)	0.131
Tracheotomy	0	5(7.1)	0.363
Tracheotomy time	0(0,0)	0(0,0)	0.419
Indwelling gastric tube	9 (81.8)	41(58.6)	0.143
Indwelling time ofgastric tube	15.09±13.247	7(0,21)	0.242
Indwelling catheter	0	37(52.9)	0.03
Indwelling catheter time	12 (7, 30)	4(0,20)	0.036

Central venous catheter	10(90.9)	37(52.9)	0.018
Indwelling time of central venous catheter	12.55±10.241	4(0,17.25)	0.169
Operation	2(18.2)	26(37.1)	0.222
β-lactams and enzyme Inhibitors	7(63.6)	33(47.1)	0.312
Carbapenem	2(18.2)	30(42.9)	0.122
Hormone	1(9.1)	28(40)	0.048
Hormone use time	0(0,0)	0(0,9.25)	0.072

Forest map of death of patients with single Candida albicans bloodstream infection and lower respiratory tract infection. Fig.4:

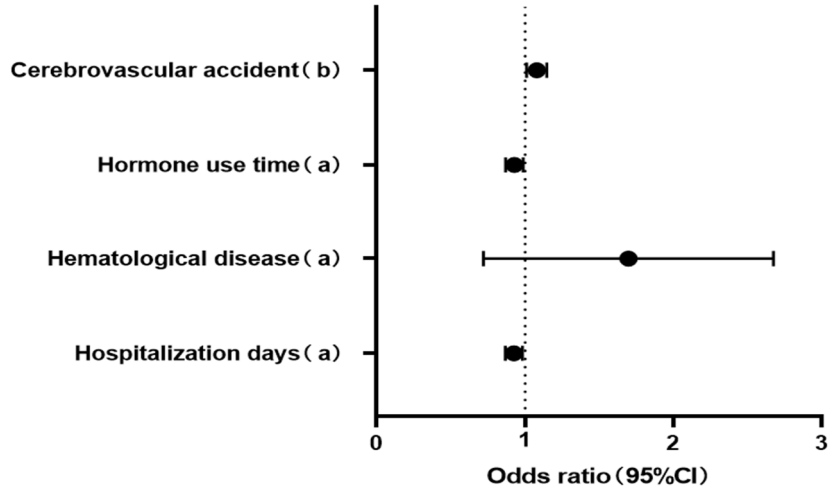


Fig 4. a: Single Candida albicans lower respiratory tract infection; b: Single Candida albicans bloodstream infection

4. Discussion

This is a 3-year multicenter retrospective study of patients with single Candida albicans bloodstream infection and lower respiratory tract infection in a tertiary teaching hospital in China. We analyzed clinical features, including demography, complications, risk factors, and patient prognosis, as well as epidemiological comparisons between patients with single Candida albicans bloodstream infection and lower respiratory tract infection. Our data showed that there was no significant difference in hospitalization days and 30-day mortality between patients with single Candida albicans bloodstream infection and lower respiratory tract infection ($P > 0.05$). Our data are consistent with other studies in adult patients with Candida albicans bloodstream infection and lower respiratory tract infection. Except for COPD and hematological malignant tumors there was no significant difference in the proportion of complications between patients with single Candida albicans bloodstream infection and lower respiratory tract infection ($P > 0.05$). The proportion of COPD in patients with single Candida albicans bloodstream infection was lower than that in patients with Candida albicans lower respiratory tract infection. The proportion of hematological malignant tumors in patients with single Candida albicans bloodstream infection was higher than that in patients with Candida albicans lower respiratory tract infection. In invasive operation, the risk of tracheotomy and CVC in patients with single Candida albicans bloodstream infection was higher than that in patients with Candida albicans lower respiratory tract infection. It is consistent with the previous research[13, 14]. During the treatment, the proportion of carbapenem antibiotics in patients with single Candida albicans bloodstream infection was higher than that in patients with Candida albicans lower respiratory tract infection ($P < 0.05$). Our data show that the number of female patients with single Candida albicans bloodstream infection is higher than that of patients with Candida albicans lower respiratory tract infection, which is different from the results of other studies. However, the male proportion is similar to that of other studies[15, 16]. In addition, this study shows that patients with single Candida albicans bloodstream infection stay longer than patients with Candida albicans lower respiratory tract infection, which is consistent with other studies[17]. The 30-day mortality rate of this study is similar to that of some hospitals in other countries, but lower than that of some other hospitals in other countries[13]. The reason may be the high sensitivity of Candida infection to antifungal drugs in this area, which may also be one of the reasons for the low mortality rate of Candida infection in this region.

In this study, length of stay, hematological malignancy, use of gastric tube and urinary catheter were common predictors of mortality in patients with single Candida albicans bloodstream infection in multivariate analysis, and univariate predictors of outcome in patients with single Candida albicans bloodstream infection were more than those in patients with lower respiratory tract infection alone (3 vs.1 predictors), as shown in Fig.4.Cancer patients constitute a large population at potential risk of Candida infection, especially hematological malignancies[18]. A big challenge for clinicians is the occurrence of fungal infections in cancer patients during treatment overshoot. Candida albicans infection can aggravate the prognosis of malignant diseases (30-day mortality is as high as 56%)[19]. High-dose chemotherapy,

mucosal barrier damage and immune system damage caused by potential malignant tumors are insurmountable risk factors for patients with Candida albicans infection. However, prophylactic use of antibiotics and widespread use of antifungal drugs after suspected fungal infection may help to determine the epidemiology of isolates. Our study is consistent with previous studies that hematological malignant tumors are a risk factor for adult patients with Candida albicans bloodstream infection. The immune function of patients with hematological malignant tumors is low, mucosal barrier is damaged by high-dose drugs, bone marrow suppression may occur after chemotherapy, stem cell transplantation, the use of immunosuppressants, the use of high-dose antibiotics and other reasons, patients with hematological malignant tumors are more likely to develop Candida bloodstream infection than patients with non-malignant hematological diseases. In recent years, although antifungal drugs have been widely used in patients with hematological diseases, the incidence of fungi is still increasing year by year. Timely and appropriate antifungal therapy is the key to the treatment of Candida bloodstream infection, and delayed empirical antifungal therapy has been reported as an independent risk factor for high mortality in patients with Candida bloodstream infection. In previous studies, only 11% of patients with Candida bloodstream infection received appropriate antifungal treatment[20]. In this study, 87.7% of patients with Candida bloodstream infection received antifungal therapy and found that these patients had a low mortality rate. In this study, antibiotic exposure was a risk factor for bloodstream infection of Candida albicans. The study reported that about 71% of patients were treated with antibiotics before Candida bloodstream infection, which was higher than in our study. The most commonly used antibiotics in this study are β-lactam. Recent studies have shown that administration of β-lactam antibiotics can lead to the release of bacteriopeptide polysaccharide subunits, including cytotoxins, which can induce invasive fungal diseases in the intestinal tract[21]. This antibiotic-induced invasion, abnormal immune system, changes in microbiome and / or changes in mucocutaneous barrier integrity make Candida albicans a conditional pathogen in the context of a series of virulence determinants[22]. Antibiotics kill not only pathogens, but also normal symbiotic microbes. Micro-ecosystems maintain balance under mutual restriction. Patients sometimes lead to Candida bloodstream infection due to the widespread use of broad-spectrum antibiotics, such as Candida colonization, and when using high-dose broad-spectrum antibiotics, drug-resistant strains can proliferate into dominant bacteria without competition, resulting in double infection. This study showed that most patients were treated with broad-spectrum antibiotics before Candida albicans bloodstream infection. This study also showed that the time of hormone use in Candida albicans group was related to Candida albicans bloodstream infection. Candida bloodstream infection is associated with increased morbidity and mortality in patients with low immune function. Length of stay (OR:0.924) and duration of hormone use (OR: 0.927) are protective factors of 30-day mortality in patients with single Candida albicans bloodstream infection. This study is consistent with Sbrana et al's study that there is a significant relationship between the prognosis of patients with Candida albicans bloodstream infection and the length of stay. Previous studies reported that respiratory dysfunction (OR: 22.57) was an independent predictor[23]. However, the length of stay (OR:0.89) and other invasive catheters (OR: 0.04) reported here are rarely reported in other studies, possibly because the demographic characteristics, underlying diseases, and risk factors of patients in our study are different from those in other studies. This may be why the independent predictors and protective factors in this study are different from those in other studies Fig.4.

In the univariate analysis of patients with Candida albicans lower respiratory tract infection, cerebrovascular accident was a common predictor of 30-day mortality ($P < 0.05$). "Cerebrovascular accident" (cerebralvascularaccident, CVA) is a disease in which cerebral blood flow is interrupted by rupture or obstruction of cerebral vessels, resulting in brain tissue damage. Cerebrovascular accident is a common and frequently-occurring disease in middle-aged and elderly patients. the invasive operation of respiratory tract in middle-aged and elderly patients often leads to the damage of respiratory tract local defense barrier function. the adhesion and removal ability of respiratory mucosal epithelial cells to foreign bodies decreased, and the cough reflex of elderly patients was weaker than that of normal adults, and secretions were easy to accumulate in the respiratory tract, resulting in Candida colonization in the respiratory tract. Even the further formation of Candida pneumonia, which eventually leads to death, the diagnosis of Candida albicans pneumonia is challenging, requiring a high suspicion index to select high-risk patients for early empirical treatment, in order to reduce mortality. However, other studies have reported that corticosteroids (OR:5.31) and septic shock (OR:5.81) in the past 30 days are independent predictors of 30-day mortality, considering that corticosteroids affect host immune response to strains by preventing macrophages from killing swallowed spores and passivating macrophages to produce pro-inflammatory cytokines (such as IL-1a and TNF-a) and chemokines (MIP-1a). These factors are important for recruiting neutrophils and monocytes[24].

This study has two potential limitations. First of all, we only have general clinical data on patients with Candida albicans infection, but no data on drug sensitivity. Secondly, although we have conducted a multicenter retrospective study, our total sample size is still small. Our data may be affected by insufficient sample size. Therefore, the results may not be extended to patients with persistent candidiasis in other parts of China.

edited the subsequent versions of the manuscript. All authors contributed to the article and approved the submitted version

Reference

1. Fisher M C, Hawkins N J, Sanglard D, et al. Worldwide emergence of resistance to antifungal drugs challenges human health and food security[J]. Science,2018,360(6390):739-742.

2. Samaranayake L P, Fidel P L, Naglik J R, et al. Fungal infections associated with HIV infection[J]. Oral Dis,2002,8 Suppl 2:151-160.
3. Kojic E M, Darouiche R O. Candida infections of medical devices[J]. Clin Microbiol Rev,2004,17(2):255-267.
4. Pfaller M A, Diekema D J. Epidemiology of invasive mycoses in North America[J]. Crit Rev Microbiol,2010,36(1):1-53.
5. Pfaller M A, Diekema D J, Turnidge J D, et al. Twenty Years of the SENTRY Antifungal Surveillance Program: Results for Candida Species From 1997-2016[J]. Open Forum Infect Dis,2019,6(Suppl 1):S79-S94.
6. Silver P M, Oliver B G, White T C. Role of Candida albicans transcription factor Upc2p in drug resistance and sterol metabolism[J]. Eukaryot Cell,2004,3(6):1391-1397.
7. Brown G D, Denning D W, Levitz S M. Tackling human fungal infections[J]. Science,2012,336(6082):647.
8. Rentz A M, Halpern M T, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness[J]. Clin Infect Dis,1998,27(4):781-788.
9. Labelle A J, Micek S T, Roubinian N, et al. Treatment-related risk factors for hospital mortality in Candida bloodstream infections[J]. Crit Care Med,2008,36(11):2967-2972.
10. Osoba A O, Al-Mowallad A W, Mcalear D E, et al. Candidemia and the susceptibility pattern of Candida isolates in blood[J]. Saudi Med J,2003,24(10):1060-1063.
11. Al-Dorzi H M, Sakkijha H, Khan R, et al. Invasive Candidiasis in Critically Ill Patients: A Prospective Cohort Study in Two Tertiary Care Centers[J]. J Intensive Care Med,2020,35(6):542-553.
12. Roux D, Gaudry S, Khoy-Ear L, et al. Airway fungal colonization compromises the immune system allowing bacterial pneumonia to prevail[J]. Crit Care Med,2013,41(9):e191-e199.
13. Rajendran R, Sherry L, Nile C J, et al. Biofilm formation is a risk factor for mortality in patients with Candida albicans bloodstream infection-Scotland, 2012-2013[J]. Clin Microbiol Infect,2016,22(1):87-93.
14. Morrell M, Fraser V J, Kollef M H. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality[J]. Antimicrob Agents Chemother,2005,49(9):3640-3645.
15. Bouza E, Burillo A, Munoz P, et al. Mixed bloodstream infections involving bacteria and Candida spp[J]. J Antimicrob Chemother,2013,68(8):1881-1888.
16. Toda M, Williams S R, Berkow E L, et al. Population-Based Active Surveillance for Culture-Confirmed Candidemia - Four Sites, United States, 2012-2016[J]. MMWR Surveill Summ,2019,68(8):1-15.
17. Chen X C, Xu J, Wu D P. Clinical characteristics and implications of mixed candida/bacterial bloodstream infections in patients with hematological diseases[J]. Eur J Clin Microbiol Infect Dis,2020,39(8):1445-1452.
18. Citiulo F, Jacobsen I D, Miramon P, et al. Candida albicans scavenges host zinc via Pra1 during endothelial invasion[J]. PLoS Pathog,2012,8(6):e1002777.
19. Luo S, Dasari P, Reiher N, et al. The secreted Candida albicans protein Pra1 disrupts host defense by broadly targeting and blocking complement C3 and C3 activation fragments[J]. Mol Immunol,2018,93:266-277.
20. Luo S, Dasari P, Reiher N, et al. The secreted Candida albicans protein Pra1 disrupts host defense by broadly targeting and blocking complement C3 and C3 activation fragments[J]. Mol Immunol,2018,93:266-277.
21. Fourie R, Kuloyo O O, Mochochoko B M, et al. Iron at the Centre of Candida albicans Interactions[J]. Front Cell Infect Microbiol,2018,8:185.
22. Ramanan N, Wang Y. A high-affinity iron permease essential for Candida albicans virulence[J]. Science,2000,288(5468):1062-1064.
23. Li L, Liao Z, Yang Y, et al. Metabolomic profiling for the identification of potential biomarkers involved in a laboratory azole resistance in Candida albicans[J]. PLoS One,2018,13(2):e192328.
24. Kimura S I, Kameda K, Harada K, et al. Risk and Predictive Factors for Candidemia After Allogeneic Hematopoietic Cell Transplantation: JSTCT Transplant Complications Working Group[J]. Transplant Cell Ther,2022,28(4):201-209.