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Epidemiology and risk factors of candidemia due to *Candida parapsilosis* in an intensive care unit

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ABSTRACT

We analyzed the clinical features and risk factors of candidemia due to *C. parapsilosis* (n=104) in the intensive care unit of a tertiary hospital over six years. This was a monocentric, retrospective study of candidemia, conducted from January 2013 to March 2019. Epidemiological characteristics, clinical features, invasive procedures, laboratory data and outcomes of 267 patients with candidemia were analyzed to determine risk factors of candidemia due to *C. parapsilosis.* Sixty-three cases of *C. albicans* and 204 cases of non-*C. albicans Candida* (NCAC) species were included, the latter was composed of 104 cases of *C. parapsilosis* and 100 cases of non-*C. albicans* species (46 cases of *C. tropicalis*, 22 cases of *C. glabrata*, 23 cases of *C. guilliermondii,* 5 cases of *C. krusei* and 4 cases of *C. lusitaniae*), suggesting that *C. parapsilosis* was the predominant *Candida s*pecies isolated from cases of candidemia. A binary multivariate logistic regression analysis showed that APACHE II scores, central venous catheterization and the use of broad-spectrum antibiotics were closely related to *C. parapsilosis* candidemia, with OR values of 1.159, 3.913 and 2.217, respectively. In conclusion, we found that *C. parapsilosis* was the main pathogen among the NCAC candidemia in the ICU patients. APACHE II scores, central venous catheterization and the use of broad-spectrum antibiotics were independent risk factors for the occurrence of *C. parapsilosis* candidemia, which may provide data to support the early introduction of anti-fungal therapy.

KEYWORDS: *Candida parapsilosis*. *Candida* spp. Candidemia. Risk factor.

INTRODUCTION

Candida albicans (*C. albicans*) is the most common known pathogen of invasive infections in adult non-neutropenic Intensive Care Unit (ICU) patients, causing roughly 70% of candidemia[1,2], increasing the length of stay in either the ICU or the hospital, with an attributable mortality rate varying from 35% to 50%[3,4]. However, in recent years, there has been a gradually increase in the incidence of candidemia caused by non-*C. albicans* species[5-7], especially of *Candida parapsilosis* (*C. parapsilosis*)[8-10], which is reported as the second most commonly isolated *Candida* spp. from blood cultures (Figure 1), even outranking *C. albicans* and becoming the most important pathogens in candidemia cases[11,12]. More and more attention has been paid on its clinical features and pathogenesis by healthcare workers and experts.

Some studies suggest that the increasing incidence of *C. parapsilosis* candidemia is related to the characteristics of the treatment regimen (such as long-term hospitalization), microorganism-related properties (its specific affinity with the surface of intravascular devices and certain prosthetic materials or plastics to form

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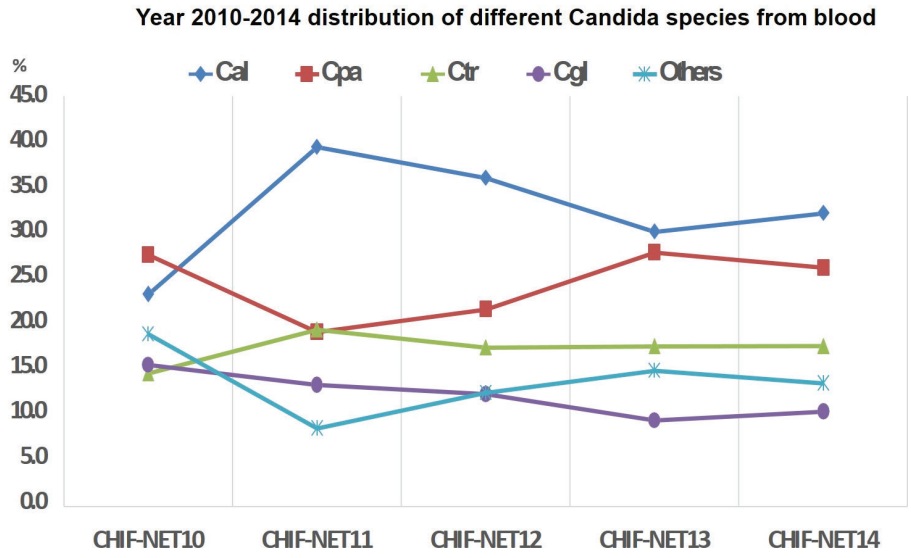

Figure 1 - Summary of 2014 data of CHIF-NET. The graphic indicated the incidence of different Candida species from blood in 5 years (2010-2014) published in China-Hospital-Invasive-Fungal-Surveillance-NET.

biofilms), and high glucose and fat environments favoring the gastrointestinal colonization and transmission[5,13-16]. Adhesion and biofilm formation are very important factors for *C. parapsilosis* indwelling on devices which appear to be the predominant route of infection[15]. The majority of patients with *C. parapsilosis* candidemia reported so far presented with underlying co-morbidities that required the use of intravenous indwelling catheters and total parenteral nutrition[16]. However, most of the studies were frequently small in size and covered a short period of time. Because of the increasing trend and the importance of *C. parapsilosis* to healthcare, our study intended to determine the risk factors of *C. parapsilosis* candidemia compared with those due to *C. albicans* and other non-*C. albicans* species in ICU wards of a large tertiary hospital in Hubei province, China.

MATERIALS AND METHODS

Study design

Clinical data were collected from patients with candidemia in ICU wards of a large tertiary hospital in Hubei, China, from January 2013 to March 2019. A total of 267 patients with candidemia were enrolled. The study protocol was reviewed and approved by the Committee for the Protection of Human Subjects at the Renmin Hospital of Wuhan University (RHWU).

Definitions

All cases met the diagnostic criteria of the Centers for Disease Control and Prevention (CDC)[17]. They were reported by the Department of Clinical Microbiology Laboratory, and the species causing candidemia were identified using the IVD MALDI Biotyper mass spectrometry (Bruker, Germany). Inclusion criteria were: (1) A patient who developed signs or symptoms of blood stream infection (BSI) > 48 h after ICU admission. (2) Laboratory microbiological examination with at least one positive blood culture to *Candida* spp. and samples to perform blood cultures drawn from either a central venous catheter or a peripheral vein/artery. If the same patient had multiple episodes of candidemia during the study period, only the first episode of candidemia was included. (3) Presence of other signs or symptoms suggestive of systemic infections: fever > 38 °C, chills, hypotension, multiple organ dysfunction, etc. Exclusion criteria: (1) Age < 18 years; (2) Suspected candidemia occurred before ICU admission; (3) Transfer, death, or central venous catheter duration < 48 h after ICU admission.

Data collection for risk factors

In our study, 267 candidemia patients hospitalized in the ICU were included. All patients were retrospectively assessed for risk factors associated with candidemia. For all the identified patients, we performed a detailed medical record review and retrieved data from the electronic medical records and reports from the RHWU Clinical Microbiology Laboratory. Briefly, we need to collect demographic data, clinical data such as host factors, medical interventions and laboratory data. Host factors included age, gender, underlying diseases (comorbidities) such as lung disease, circulatory system disease, neoplastic

disease, kidney disease, liver disease, etc., the APACHE II Score (Acute physiology and chronic health evaluation) within 24 h after ICU admission, ICU length of stay, and outcome. Retrieved medical interventions included total parenteral nutrition (TPN), mechanical ventilation (MV), prior use of medications (broad-spectrum antibiotics, hormones, immunosuppressants, etc.), abdominal surgeries, intravascular catheterization location (jugular, subclavian and femoral) and duration (> 5 days) considering the risks of infections and the time required by *Candida* spp. to adhere, colonize and form mature biofilms. Laboratory data included the patients' immune status (presence or absence of neutropenia), G test results, coinfections with bacteria and different organs disfunctions.

Statistical analysis

Categorical variables were compared by the chi square test or the Fisher exact test (SPSS Version 20.0, IBM, Armonk, NY, USA). Odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the strength of selected associations. Continuous variables were compared using the Wilcoxon rank sum test. A two-tailed *p*-value of < 0.05 was considered significant. A multivariate logistic regression analysis was performed to identify associations between variables and risk factors to develop candidemia due to *C. parapsilosis* compared to other *Candida* species. Besides the multi-collinearity among some variables in the multivariate analysis, variables with a univariate *p*-value < 0.1 were considered for the inclusion in the multivariate model.

RESULTS

During the 6-year study period 2013-2019, 267 candidemia patients were enrolled at RHWU (Figure 2). All the included patients were divided into groups: *C. albicans*, *C. parapsilosis* and other non-*C. albicans* species group.

Species distribution

Among the detected 267 patients with candidemia, 63 (23.6%) were caused by *C. albicans*, 104 (39.0%) by *C. parapsilosis* and 100 (37.4%) by other non-*C. albicans* species, include 46 (17.2%) cases of *C. tropicalis*, 22 (8.2%) cases of *C. glabrata*, 23 (8.6%) cases of *C. guilliermondii*, 5 (1.9%) cases of *C. krusei* and 4 (1.5%) cases of *C. lusitaniae* (Table 1). The total number of isolates of non-*C. albicans* species was 204 (76.4%). The most common isolated species were *C. parapsilosis*, followed by *C. albicans*, *C. tropicalis, C. guilliermondii*, *C. glabrata* and *C. krusei*.

Table 1 - Distribution of different *Candida* species.

Species	Number (%)
C. albicans	63 (23.6)
C. parapsilosis	104 (39.0)
Other non-*Candida albicans* species	100 (37.4)
C. tropicalis	46 (17.2)
C. glabrata	22 (8.2)
C. guilliermondii	23 (8.6)
C. krusei	5 (1.9)
C. lusitaniae	4 (1.5)

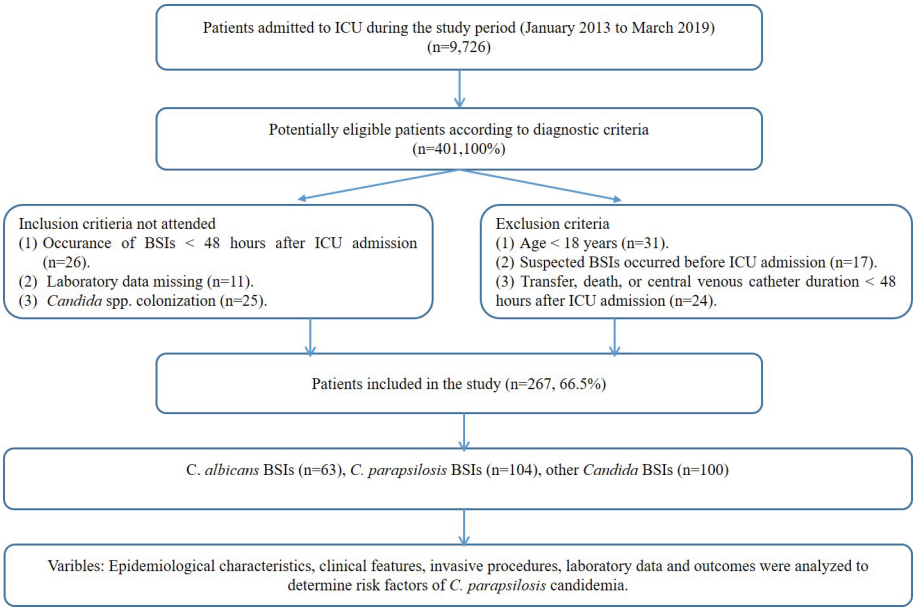

Figure 2 - Flow diagram. The graphic described the diagnostic criteria, inclusion criteria and exclusion criteria, how many patients were included and explained why.

Demographic characteristics of patients with different species of candidemia are shown in Table 2. One hundred and twenty one (45.3%) patients were male and the mean age of patients was 58.12 ± 16.51 years. In the *C. albicans* group, 33 patients were male and 30 patients were female, the mean age was 61.41 ± 15.98 years, while in the non-*C. albicans* species group, 88 (33.0%) patients were male and 116 (43.4%) patients were female, and the mean age was 57.11 ± 16.58 years. Regarding gender and age, no significant differences were found between patients with candidemia due to *C. parapsilosis* and other *Candida* species.

To investigate the correlation between severity of illness and episodes of candidemia caused by *C. parapsilosis*, we found that the mean of APACHE II Scores in all groups was above 20. In the *C. albicans* group, the mean of APACHE II Score was 21.71±3.21; 25.85±6.08 in the *C. parapsilosis* group and 22.33±4.90 in the group of other non-*C. albicans* species. We found that the APACHE II Score of patients with *C. parapsilosis* candidemia episodes was higher than in both groups of *C. albicans* and other non-*C. albicans* species (p=0.000). These results are shown in Table 2.

Relationship between the presence of underlying diseases (comorbidities) and episodes of candidemia caused by different *Candida* species

We investigated the presence of underlying diseases (comorbidities) and the main diagnosis of the enrolled ICU patients. There were 16 cases of type 2 diabetes, 14 cases of renal insufficiency, 20 patients with hypertension, 13 cases of heart disease, 10 cases of chronic obstructive pulmonary disease, 13 cases of cerebral ischemia, 3 cases of cirrhosis, 3 cases of congenital heart disease, 8 cases of neoplastic disease, 2 cases of autoimmune disease and 35 cases of comorbidities involving more than 2 systems. There were no significant differences in the frequency of comorbidities and the major causes of ICU admission among groups of candidemia by *C. albicans*, *C. parapsilosis* and other non-*C. albicans* species. These results are shown in Table 2.

Relationship between the use of medical interventions and the presence of episodes of candidemia caused by different *Candida* species

Of the 267 patients, 124 (46.4%) cases were placed with a central venous catheter (double-lumen), of which 21 cases were in *C. albicans* group, 75 cases were in *C. parapsilosis* group, and 28 cases were in other non-*C. albicans* species group. Regarding the catheter location, there were 48 cases of subclavian vein catheterization (six cases in *C. albicans* group, 32 cases in *C. parapsilosis* group, and 10 cases in other groups), 35 cases of internal jugular vein catheterization (ten cases in *C. albicans* group, 16 cases in *C. parapsilosis* group, and nine cases in other groups), 57 cases of femoral vein catheterization (nine cases in *C. albicans* group, 34 cases in *C. parapsilosis* group,

Table 2 - Comparison of epidemiological characteristics of patients hospitalized in an intensive care unit presenting with infections caused by different species of *Candida.*

Variables*	*C. albicans* (n=63)	*C. parapsilosis* (n=104)	Others# (n=100)	*P*
Age (years) (Mean ± SD)	61.41±15.98	57.02±15.51	57.20±17.69	> 0.05
Gender (Male)	33 (52.4)	46 (44.2)	42 (42.0)	> 0.05
Comorbidities	25 (39.7)	33 (31.7)	44 (44.0)	
Type 2 diabetes	4 (6.3)	5 (4.8)	7 (7.0)	
Renal insufficiency	4 (6.3)	4 (3.8)	6 (6.0)	
Hypertension	5 (7.9)	6 (5.8)	9 (9.0)	
Coronary heart disease	4 (6.3)	4 (3.8)	5 (5.0)	
COPD	2 (3.2)	4 (3.8)	4 (4.0)	
Cerebral ischemia	2 (3.2)	5 (4.8)	6 (6.0)	> 0.05
Cirrhosis	-	-	3 (3.0)	
Congenital heart disease	2 (3.2)	1 (0.96)	-	
Neoplastic disease	2 (3.2)	3 (2.9)	3 (3.0)	
Autoimmune disease	-	1 (0.96)	1 (1.0)	
> 2 systems diseases	9 (14.3)	15 (14.4)	11 (11.0)	
APACHE II Score	21.71±3.21	25.85±6.08[a]	22.33±4.90	**0.000**
ICU length of stay (days)	14.38±8.05	14.13±7.50	12.98±7.73	> 0.05
Mortality	5 (7.9)	12 (11.5)[a]	8 (8.0)	**0.046**

*Values for all variables except age, APACHE II Scores and ICU-stay are given in percentages of patients; #All *Candida* species other than *C. albicans* or *C. parapsilosis* included 46 *C. tropicalis*, 22 *C. glabrata*, 23 *C. guilliermondii*, 5 *C. krusei* and 4 *C. lusitaniae*; SD = Standard deviation; APACHE = Acute Physiology and Chronic Health Evaluation; ICU = Intensive Care Unit; COPD = Chronic obstructive pulmonary disease; [a]*P* <0.05, significant difference between between *C. parapsilosis* and Others (*C. parapsilosis vs* Others).

14 cases in other groups), and eight cases of basilic vein catheterization (one case in *C. albicans* group, five cases in *C. parapsilosis* group, two cases in other groups). Among them, 24 patients had catheters in both, the jugular vein or the subclavian vein or the basilic vein and the femoral vein (four cases in *C. albicans* group, 13 cases in *C. parapsilosis* group, and seven cases in non-*C. albicans* species group). We found that the presence of central venous catheters, the CVC duration > 5 days and the catheterization locations in the subclavian and the femoral vein, were significant different between *C. parapsilosis*, *C. albicans* and the other non-*C. albicans* species group (p=0.000; 0.024; 0.000; 0.002). These results are shown in Table 3.

It has been reported that total parenteral nutrition (TPN) is an important factor of biofilm formation. We examined the total parenteral nutrition > 3 days in the different *Candida* species groups and found that differences were significant between *C. parapsilosis*, *C. albicans* and other non-*C. albicans* species (p=0.000). These results are shown in Table 3.

In respect to the prior risk factors (reported before the ICU hospitalization), we checked the use of broad-spectrum antibiotics in the different *Candida* species groups and found that there was a significant difference between *C. albicans* and other non-*C. albicans* species (p=0.000), also between *C. albicans* and *C. parapsilosis* (p=0.000). Considering the mechanical ventilation, there was a significant difference between *C. parapsilosis*, *C. albicans* and other non-*C. albicans* species (p=0.000; 0.046) groups. These results are shown in Table 3.

Comparison of laboratory data of different species causing candidemia

We investigated some important clinical parameters including neutropenia, positivity of the G test (1,3-β-D-Glucan [BDG]) test. which is a fungal cell wall constituent used in the diagnosis of invasive fungal infections), the presence of multiple organ dysfunction syndrome (MODS) and coinfections. Through these comparisons, we found that there were no significant differences among groups of *C. albicans*, *C. parapsilosis* and other non-*C. albicans* species. These results are shown in Table 4.

Risk factors associated with *C. parapsilosis* candidemia

Relevant risk factors included in the analysis of *C. parapsilosis* bloodstream infections were gender, age, underlying diseases (comorbidities), the APACHE II score, the ICU length of stay (days), mortality, use of broad-spectrum antibiotics, use of steroids and immunosuppressants, CVC placement and location, catheterization duration > 5 days, use of total parenteral nutrition (TPN) > 3 days, special medical interventions such as continuous renal replacement therapy (CRRT), mechanical ventilation, abdominal surgeries, clinical data

Table 3 - Comparison of the relationship between different species of *Candida* infections and medical interventions.

Variables*	*C. albicans* (n=63)	*C. parapsilosis* (n=104)	Others# (n=100)	95% CI	*P*
Broad-spectrum antibiotics	30 (47.6)[a]	76 (73.1)	73 (73.0)	0.338-0.554	0.000
Steroids	2 (3.2)	4 (3.8)	5 (5.0)	-	> 0.05
Immunosuppressants	0 (0.0)	0 (0.0)	1 (1.0)	-	-
Central venous catheter	21 (33.3)	75 (72.1)[b]	28 (28.0)	0.277-0.530	**0.000**
Internal jugular	10 (15.9)	16 (15.4)	9 (9.0)	-	> 0.05
Subclavian vein	6(9.5)	32 (30.8)[b]	10 (10.0)	0.099-0.316	**0.000**
Femoral vein	9 (14.3)	34 (32.7)[b]	14 (14.0)	0.072-0.302	**0.002**
Basilic vein	1 (1.6)	5 (4.8)	2 (2.0)	-	> 0.05
CVC duration >5 days	14 (22.2)	45 (43.3)[b]	2 3(23.0)	0.019-0.271	**0.024**
Total parenteral nutrition >3 days	21 (33.3)	72 (69.2)[b]	42 (42.0)	0.140-0.405	**0.000**
Mechanical ventilation	30 (47.6)[a]	69 (66.3)[b]	32 (32.0)	0.003-0309 0.213-0.474	**0.046** **0.000**
Continuous renal replacement therapy	11 (17.5)	21 (20.2)	13 (13.0)	-	> 0.05
Abdominal surgeries	16 (25.4)	27 (26.0)	26 (26.0)	-	> 0.05

*Values for all variables are given in percentages of patients; #All Candida species other than *C. albicans* or *C. parapsilosis* included 46 *C. tropicalis*, 22 *C. glabrata*, 23 *C. guilliermondii*, 5 *C. krusei* and 4 *C. lusitaniae*; CVC = Central venous catheter; [a]P<0.05, significant difference between *C. albicans* and other *Candida* species (*C. albicans vs* Others); [b]P<0.05, significant difference between *C. parapsilosis* and other *Candida* species (*C. parapsilosis vs* Others).

Table 4 - Comparison of laboratory data of different species of *Candida* causing infections.

Variables*	*C. albicans* (n=63)	*C. parapsilosis* (n=104)	Others# (n=100)	*P*
Neutropenia	0 (0.0)	3 (2.8)	0 (0.0)	> 0.05
Positive G test	25 (39.7)	39 (37.5)	38 (38.0)	> 0.05
MODS	20 (31.7)	35 (33.7)	41 (41.0)	> 0.05
Coinfection	28 (44.4)	38 (36.5)	39 (39.0)	> 0.05

*Values for all variables are given in percentages of patients; #All Candida species other than *C. albicans* or *C. parapsilosis* included 46 *C. tropicalis*, 22 *C. glabrata*, 23 *C. guilliermondii*, 5 *C. krusei* and 4 *C. lusitaniae*; MODS = Multiple organ dysfunction syndrome.

such as neutropenia, positivity of the G test, the multiple organ dysfunction syndrome (MODS), coinfections with other bacteria (mainly Gram-positive / negative bacteria).

An univariate analysis was performed on the variables, searching for possible risk factors of *C. parapsilosis* bloodstream infections. The results showed that the APACHE II Score, therapy with broad-spectrum antibiotics, the presence of a central venous catheter, catheterization locations and duration, total parenteral nutrition > 3 days and mechanical ventilation were all risk factors for *C. parapsilosis* bloodstream infection (p=0.000; 0.001; 0.000; 0.003; 0.013; 0.009; 0.000; 0.029). Regarding to the ICU length of stay, CRRT treatment, abdominal surgeries, neutropenia, a positive G test, MODS and coinfections were not significantly related to the occurrence of *C. parapsilosis* bloodstream infections (p> 0.05). Results are shown in Table 5. To further analyze variables in the univariate analysis (Table 5), a multivariate regression analysis was performed. Considering multi-collinearity in the multivariate analysis, it was found that mechanical ventilation was a confounding factor (p> 0.05), while the APACHE II score, CVC catheterization, and the use of broad-spectrum antibiotics were closely related to *C. parapsilosis* bloodstream infections (p=0.001;

Table 5 - Risk factors for *C. parapsilosis* bloodstream infections after single parameter analysis.

	B	Wald	OR (95% CI)	*P*
Age (year) (Mean ± SD)	-0.015	2.184	0.985 (0.965-1.005)	0.139
Gender (Male)	-0.275	0.733	0.760 (0.405-1.425)	0.392
Underlying comorbidities	-0.277	0.687	0.758 (0.394-1.459)	0.407
APACHE II Scores	0.164	19.157	1.179 (1.095-1.268)	**0.000**
ICU length of stay (days)	-0.008	0.156	0.992 (0.952-1.033)	0.693
Mortality	0.386	0.478	1.471 (0.493-4.393)	0.498
Central venous catheter	1.585	21.178	**4.881 (2.485-9.588)**	**0.000**
Internal jugular catheter	-0.067	0.024	0.935 (0.395-2.211)	0.878
Subclavian vein catheterization	1.409	8.650	4.091 (1.600-10.462)	**0.003**
Femoral vein catheterization	1.037	6.196	2.820 (1.247-6.739)	**0.013**
Basilic vein catheterization	1.115	1.014	3.050 (0.348-26.727)	0.314
Broad-spectrum antibiotics	1.141	11.468	3.129 (1.617-6.056)	**0.001**
Steroids	0.172	0.038	1.188 (0.211-6.683)	0.845
CVC duration > 5 days	0.944	6.801	2.571 (1.264-5.229)	0.009
Total parenteral nutrition > 3 days	1.449	18.074	4.260 (2.184-8.309)	0.000
Mechanical ventilation	0.715	4.768	2.044 (1.077-3.880)	**0.029**
Continuous renal replacement therapy	0.148	0.128	1.159 (0.517-2.601)	0.720
Abdominal surgeries	-0.005	0.000	0.995 (0.486-2.040)	0.989
Positive G test	-0.134	0.167	0.875 (0.459-1.664)	0.683
MODS	0.049	0.020	1.050 (0.538-2.051)	0.886
Coinfection	-0.267	0.668	0.766 (0.404-1.452)	0.414

B = Coefficient estimates; Wald: Chi-square value; OR: Odds ratio; CI = Confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation; CVC = Central venous catheter.

Table 6 - Risk factors in the multivariate analysis of *C. parapsilosis* bloodstream infections.

	B	Wald	OR (95% CI)	*P*
APACHE II Scores	0.148	11.969	1.159 (1.066- 1.261)	**0.001**
Central venous catheter	1.364	11.978	3.913 (1.807- 8.474)	**0.001**
Broad-spectrum antibiotics	0.796	4.233	2.217 (1.038- 4.734)	**0.040**

B = Coefficient estimates; Wald = Chi-square value; OR = Odds ratio; CI = Confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation.

0.001; 0.040), with OR values of 1.159, 3.913 and 2.217, respectively. Results are shown in Table 6.

Treatment and prognosis

The main treatment measures included removal of the central venous catheters and antifungal therapy. Echinocandins (micafungin, caspofungin) were used as previously recommended[3]. In two cases, the central catheters could not be removed or replaced. There were 25 deaths (five in *C. albicans* group, 12 in *C. parapsilosis* group, and eight in the other non-*C. albicans* groups). There was a statistical difference in mortality between the *C. parapsilosis* group and the other non-*C. albicans* species group (p=0.046), while there were no statistical differences in ICU length of stay between the groups. These results are shown in Table 2.

DISCUSSION

Candida bloodstream infections are still serious nosocomial infections worldwide and are the third or fourth causes of healthcare-related bloodstream infections[8]. *C. albicans* has been regarded as the main pathogenic fungus, however, in recent years, non-*C. albicans* species have gradually become the main pathogen of hospital-acquired candidemia[11,12]. Studies have shown that the most frequently implicated risk factors of invasive candidemia include the use of broad-spectrum antibiotics, immunossupressant agents (glucocorticosteroids, chemo-therapeutic agents, and immunomodulators), neutropenia, use of central venous catheters, total parenteral nutrition, renal replacement therapy and use of implantable prosthetic devices[18,19]. A number of studies have shown that the rate of *C. parapsilosis* isolation from blood samples or venous catheter implants is second to or higher than the rate of *C. albicans* isolation from the same sources[20,21]. In our study, a total of 267 patients with candidemia were included. Among them, *C. parapsilosis* accounted for 38.95% (104 cases) of candidemia cases, while the proportion of *C. albicans* was 23.60% (63 cases) and of other non-*C. albicans* species was 37.45% (100 cases) (Table 1). To our surprise, the proportion of candidemia attributed to *C. parapsilosis* was even higher than the one of *C. albicans* during our study period, indicating that non-*C. albicans* species are becoming the most common cause of *Candida* bloodstream infections, which is consistent with data of previous studies[11,12,21,22].

Several studies[6,8] have shown that the occurrence of candidemia is associated with increasing length of hospital stay and medical costs. Almirante *et al.*[22] found that the early and overall mortality of patients with *C. parapsilosis* candidemia was lower than those of *C. albicans* (6% vs 25%, 7 days; 23% vs 43%, overall; p< 0.01). In our study, we compared candidemia caused by different species andthe results indicated that there was no significant differences in terms of mortality and ICU length of stay compared to candidemia caused by *C. parapsilosis* and *C. albicans.*

Regarding risk factors, an observational study in Europe concluded that catheter implantation, use of broad-spectrum antibiotic, total parenteral nutrition, abdominal surgeries, glucocorticoid therapy, tumors, organ transplants, neutropenia and previous *Candida* colonization are high-risk factors for *C. parapsilosis* candidemia[22]. Our study showed that APACHE II score, CVC catheterization and use of broad-spectrum antibiotics were independent risk factors for *C. parapsilosis* candidemia (Table 6).

APACHE II is a severity-of-disease classification system proposed by Knaus *et al.*[23] that has been widely used in emergency and critical care medicine. It is determined within 24 h of admission to an ICU, with higher scores corresponding to more severe disease and a higher risk of death. In our study, the average APACHE II score of *C. parapsilosis* candidemia patients was above 25, which was significantly higher than the one of candidemia patients caused by other *Candida* species (Table 2). We can also imply that *C. parapsilosis* candidemia patients were in more severe conditions when admitted to emergency department.

It is reported that approximately 80% of patients with non-neutropenic candidemia originated from the presence of intravascular catheters, such as a central venous catheter, a hemodialysis catheter, a PICC or an implantation port. Clinically useful biological materials can easily favor *Candida* colonization and biofilm

formation, and cause related bloodstream infections[24-27]. In our study, patients with *C. parapsilosis* candidemia showed a higher rate of CVC compared with those of other *Candida* species (Table 3). An analysis of 393 cases of *Candida* spp. bloodstream infections in Switzerland, from 2005 to 2006, showed that the positive rate of biofilms in cases caused by non-*C. albicans* species (88.7%) was significantly higher than that of *C. albicans* (40.3%), while in the *C. parapsilosis* group the rate of biofilms reached 66.7%. This study indicated that the ability of *Candida* to adhere to the surface of the conduct to form a biofilm was highly strain-dependent. *C. parapsilosis* isolated from different locations have different biofilm-forming capabilities, which was the strongest when the isolates were from bloodstream cultures[28]. Studies by Branchini *et al.*[14] found that *C. parapsilosis* can proliferate in high-concentration glucose conditions and form a biofilm on the prosthetic material. The mucus production by *C. parapsilosis* helps it to fix on plastic catheters, and the biofilm formation is related to the colonization ability of *C. parapsilosis* placed on the central venous catheter, and has been considered as a virulence factor for *C. parapsilosis* candidemia. A Costa Rican clinical study found a strong association between *C. parapsilosis* candidemia and central venous catheterization and total parenteral nutrition[20]. In addition, the colonization and *C. parapsilosis* infection depend on its ability to adhere to host cell tissues, especially mucosal epithelia. As adhesion can promote the destruction of adjacent host cells by *Candida,* this adhesion in *C. parapsilosis* may be related to the presence of hydrophobic molecules on the surface of *Candida* spp.[29].

Our results indicated that the administration of broad-spectrum antibiotics was another independent risk factors for *C. parapsilosis* candidemia (Table 6). We know that empiric broad-spectrum therapy with one or more intravenous antimicrobials to cover all likely pathogens should be started immediately in patients presenting with sepsis or septic shock[30]. In the updated Surviving Sepsis Campaign (SSC) bundle of care[31], which have combined the 3-h and 6-h bundles into a single "hour-1 bundle" recommendations such as obtaining blood cultures prior to administration of antibiotics and administration of broad-spectrum antibiotics in 1 h should be accomplished within"hour-1 bundle". Once the pathogen identification and its sensitivities are established, empiric antimicrobial therapy should be narrowed or discontinued if infection is subsequently proven not to exist. The link between early administration of broad-spectrum antibiotics for suspected infection and antibiotic stewardship remains an essential aspect of high-quality sepsis management.

In short, this study analyzed the demographic characteristics, underlying comorbidities, clinical interventions and laboratory data of patients with candidemia indicating that among the pathogens that cause candidemia in ICU, *C. parapsilosis* among the non-*C. albicans* species is becoming dominant. Moreover, the results showed that APACHE II score, CVC catheterization and use of broad-spectrum antibiotics were independent risk factors for *C. parapsilosis* candidemia. Because this is a monocentric study, further multicenter studies placed in different geographical regions should perform studies on candidemia in ICU patients to better define the epidemiology and pathogenesis of candidemia, helping intensive care specialists to assess the distribution and trends in their patients with clinically suspected candidemia.

CONCLUSION

In the ICU patients with candidemia, *C. parapsilosis* is becoming the main pathogen among NCAC candidemia. APACHE II scores, central venous catheterization and use of broad-spectrum antibiotics were independent risk factors for the occurrence of *C. parapsilosis* candidemia, which may provide data to support the early anti-fungal therapy. There are several limitations in the present study. First of all, this is a retrospective clinical study which is frequently used for severe nosocomial infections with low incidence rates that may need very large sample sizes for more accurate outcome analysis. Secondly, the sample in this study was selected over 6 years, so that the testing procedures may have varied over time. However, in our study, we have not detected any variation over time. Finally, this is a monocentric study and the findings are focused on *C. parapsilosis* candidemia, so that the results can be extrapolated but with caution. Further multicenter studies can better define the epidemiology and pathogenesis of *C. parapsilosis* candidemia.

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ETHICAL APPROVAL

The protocol was approved by the medical ethics committee of the Renmin Hospital, Wuhan University.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

AUTHORS' CONTRIBUTIONS

KH conceived the project and designed the study, XSZ and YNL analyzed and interpreted the data. XSZ drafted the first draft of the manuscript. All authors revised and approved the final version of the manuscript.

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