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Candidemia in major burn patients and its possible risk factors: A 6-year period retrospective study at a burn ICU

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ARTICLE INFO

Article history:
Accepted 3 January 2019

Keywords:
Burn
Candidemia
Risk factor
T-cell lymphopenia
Drug susceptibility

ABSTRACT

Objective: The aims of this study were to evaluate the epidemiological and clinical characteristics of candidemia in a typical burn ICU, and to determine the risk factors associated with candidemia among major burn patients.

Method: This retrospective observational study of candidemia from 2012 to 2017 in a burn ICU was conducted in the Department of Burn, Southwest hospital, Chongqing, China.

Results: The study included 410 major burn patients (≥40% total body surface area), 39 (9.51%) of which were diagnosed with candidemia. The annual incidences of candidemia varied from 6.06% to 17.54%, and increased gradually in the 6 years. *Candida parapsilosis* was the dominant pathogen (28.21% strains). The overall resistance rate of *Candida* spp. to fluconazole was 35.89%. Candidemia cases most frequently occurred in the 2nd (30.77%) and 3rd (23.08%) weeks after burn, and intravascular catheters were the most common sources of bloodstream *Candida* infections (31.58%). The crude mortality of candidemia was 23.08%, and the mortality attributable to candidemia was 14.99%. Risk factors of candidemia included inhalation injury, renal dysfunction with replacement therapy, severe gastrointestinal complications, T-cell lymphopenia and prior *Candida* colonization.

Conclusion: Candidemia has a high incidence and mortality in major burn patients. The changes in etiology and drug sensitivity may make new challenges for the management of candidemia in burn ICUs.

1. Background

Severe infection remains the leading cause of death in patients with extensive burn injuries [1]. Burn patients are more vulnerable to both local and systemic infections due to the damage of the skin barrier, impaired immune function, repeated surgical interventions and long stays in the ICU [2,3]. With the early use of broad-spectrum antibacterial agents, a decrease in bacterial infection was observed in most burn units over previous decades. Nevertheless, opportunistic fungal infections represent a growing threat to burn patients.

Candida spp. represent almost 80% of nosocomial fungal infections, and are being identified as the fourth most frequent organism causing bloodstream infections in patients in intensive care units [4,5]. The incidence of candidemia was reported to range between 0.3% and 4% among burn patients depending on the characteristics of the hospital [2]. Patients in burn ICUs (BICUs) have significantly higher incidences of candidemia (4% to 11%), due to the extent of body surface burnt

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https://doi.org/10.1016/j.burns.2019.01.005

and the severity of injury [6]. And candidemia leads to a very high mortality (30% to 58%) in burn patients [7]. Therefore, the management of candidemia has a great significance to the improvement of burn care.

Nevertheless, at present there have been few studies referring to candidemia in major burn patients in China. In this context, we performed this 6-year period retrospective study to analyze the microbiology, epidemiology, risk factors, clinical therapy and outcomes of candidemia in the BICU of the largest burn center in southwest China.

2. Methods

2.1. Study design

This retrospective observational study from Jan 2012 to Dec 2017 included cases which met the following criteria: (1) patients with major burn injury (≥40% total body surface area, TBSA); (2) admission to the ICU of the Burn Department of Southwest Hospital; (3) no abandonment of therapy during 72h after admission. Clinical data of demographics, burn injury characteristics, complications, clinical situations at the time of candidemia diagnosis, risk factors, microbiological aspects, treatment and outcome were collected from the medical records. Approval was granted by the Human Medical Ethics Committees of Southwest Hospital. No personal information of patients was disclosed during the study.

2.2. Definition

Patients with the same Candida species isolated and identified from at least 2 continuous blood samples were diagnosed with candidemia according to the *guidelines of invasive fungal infection post burn injury in China (2013)* [8]. And clinical diagnosis of bacteremia was based on the American Burn Association criteria [8,9]. Candida colonization was defined as isolation of Candida species from the non-blood body sites without clinical manifestation of infection, or imaging and laboratory examination evidences [8]. Duplicates of same isolates from same body site in 14 days were not counted repeatedly. Exposure to broad-spectrum antibacterial agents refers to the administration of carbapenems, 3rd and 4th generations of cephalosporins, penicillin plus beta-lactamase inhibitor, quinolones and glycylcyclines. Prior *Candida* colonization was defined as the isolation of *Candida* spp. from at least one non-blood body site before the diagnosis of candidemia [10,11]. The gastrointestinal complications in this study include gastrointestinal perforation, cholangitis, intestinal bowel necrosis and severe gastrointestinal bleeding with surgical therapies [6]. T-cell lymphopenia was defined as peripheral blood $CD3^+$ cell counting <770/ul, or $CD3^+CD4^+$ cell counting <500/ul according to the device manufacturer's recommendation.

2.3. Microbiological studies

Microbiological cultures were incubated in automated systems (BacT/ALERT© BioMeriéux, France). Isolates were then identified to species using the Vitek-2™ Compact automatic analyzer (BioMeriéux, France). In vitro susceptibility of isolates to systemic antifungal agents was assessed using the Kirby–Bauer disk diffusion method with drug sensitive test disks (ROSCO, Denmark) strictly according to the Clinical & Laboratory Standards Institute (CLSI) standard document M44-A2 [12]. *Candida glabrata* (ATCC15126) was used as quality control strain.

2.4. Statistical analysis

Patient characteristics data were presented as the mean ±standard deviation (SD), or the median and interquartile range (IQR) according to the normality. Statistical analysis was performed using Student's t-test or Chi-squared test as appropriate. The effect of risk factors was analyzed by multivariate logistic regression. To quantify the effects, the odds ratio (OR) and 95% confidence interval (CI) were calculated. Differences of $p < 0.05$ were considered statistically significant.

3. Results

In this 6-year period retrospective study, of 449 major burn patients, 410 were included in the final analysis. The demographic and clinical characteristics were shown in Table 1.

Among the patients included in this study, 39 patients were diagnosed with candidemia, an overall incidence of 9.51% in the 6 years. The annual distribution of candidemia cases and the incidence during each year are shown in Table 2. A substantial increasing tendency in the incidence of candidemia in the 6 years could be observed.

A total of 298 strains of *Candida* spp. were isolated from the patients, including 39 strains isolated from bloodstream, and another 259 strains isolated from the non-blood body sites including wound, intravascular catheter, respiratory tract and urinary samples. On characterizing these isolates, the most common species isolated from blood samples were *C.parapsilosis* (28.21%), *C.albicans* (15.38%) and *C.tropicalis* (15.38%) (Fig. 1A). The dominant *Candida* species isolated from non-blood body sites were *C.albicans* (27.03%), *C.tropicalis* (24.71%) and *C.parapsilosis* (18.53%) (Fig. 1B).

The in vitro drug susceptibility tests showed that 14 strains (35.89%) of *Candida* spp. isolated from the blood samples were resistant or had reduced susceptibility to fluconazole (FLC). FLC resistance was observed to be the highest among *C. glabrata* (50% resistant, and 25% dose-depend susceptible), followed by *C.krusei* (40% resistant, and 20% dose-depend susceptible). The *C.tropicalis* also had a high resistance rate to all azoles. The in vitro susceptibility rate of *C.tropicalis* was only 50% to FLC or itraconazole. Even though voriconazole had excellent in vitro activity against most *Candida* spp., it showed sensitivity against 66.67% strains of C.tropicalis. All isolated strains were susceptible to echinocandins (caspofungin or micafungin) and amphotericin B (Fig. 2).

The mean number of days from burn injury until development of candidemia was 20.21±15.36. The time distribution of the candidemia cases after burn was shown in Fig. 3A. The most candidemia cases were diagnosed in the 2nd week (12 cases, 30.77%) 3rd (9 cases, 23.08%) weeks after burn, over half of the cases were diagnosed during this period.

Table 1 – Demographics and clinical characteristics of the patients.

Clinical characteristics		All patients	Candidemia	Non-candidemia
Gender	Male	299 (72.93%)	34 (87.12%)	265 (71.43%)
	Female	111 (27.07%)	5 (12.82%)	106 (28.57%)
Age (years)		37.38±18.84	41.90±18.51	36.93±17.90
Burn area (%TBSA)		61.15±20.73	59.03±25.85	62.37±19.87
Full thickness area (%TBSA)		23.48±20.27	30.66±23.78	22.97±19.98
Inhalation injury		137 (33.41%)	23 (58.97%)	114 (30.73%)
ABSI score		6.31±2.47	7.40±2.51	6.23±2.45
Tracheotomy		271 (66.10%)	23 (58.97%)	248 (66.85%)
Mechanical ventilation		162 (39.51%)	21 (53.84%)	141 (38.01%)
Central vascular catheter		374 (91.21)	37 (94.87%)	337 (90.84%)
Parenteral nutrition		344 (83.90%)	28 (71.79%)	316 (93.76%)
Renal replacement therapy		29 (7.07%)	7 (17.94%)	22 (5.93%)
Gastrointestinal complications		14 (3.41%)	4 (10.26%)	10 (2.70%)
Corticosteroids		27 (6.59%)	2 (5.12%)	25 (6.74%)
Hypotension		116 (28.29)	14 (35.90%)	102 (27.49%)
Broad-spectrum antibacterial		392 (95.61%)	38 (97.44%)	354 (95.41%)
Diabetes		47 (11.46%)	3 (7.69%)	44 (11.86%)
Prior Candida colonization		151 (36.82%)	22 (56.41%)	129 (34.77%)
Prophylactic antifungal drugs		182 (44.39%)	17 (43.58%)	165 (44.47%)
Bacteremia		224 (54.63%)	26 (66.67%)	198 (53.37%)
Mortality		40 (9.76%)	10 (23.08%)	30 (8.09%)

Abbreviations: TBSA– total body surface area, ABSI– abbreviated burn severity index.

Table 2 – Annual distribution incidence of candidemia.

Year	Number of patients	Candidemia cases	Incidence
2012	70	6	8.57%
2013	79	6	7.59%
2014	77	6	7.79%
2015	66	4	6.06%
2016	61	7	11.48%
2017	57	10	17.54%
Overall	410	39	9.51%

Intravascular catheters were recognized as the most common potential source of candidemia (12 cases, 30.77%), followed by the urinary tract (5 cases, 12.82%). Although the burn wounds had a high rate of *Candida* colonization, only 7.69% cases of candedemia were developed from the wound. Nevertheless, in 43.59% cases, the source of infection could not be determined (Fig. 3B)

Risk factors associated with candidemia included inhalation injury (OR=2.06, 95% CI=1.22–5.46, p=0.02), renal dysfunction with replacement therapy (OR=3.41, 95% CI=1.04–9.05, p=0.04), gastrointestinal complications (OR=4.97, 95% CI=1.46–17.06, p=0.01), T-cell lymphopenia (OR=1.74, 95% CI=1.28–7.84, p=0.02), and prior *Candida* colonization (OR=1.62, 95% CI=1.12–4.54, p=0.04) in this study. Gender, age, burn area, abbreviated burn severity index (ABSI) score, tracheotomy, mechanical ventilation, presence of central vascular catheter, parenteral nutrition, diabetes and bacteremia were not identified as risk factors for candidemia in major burn patients (Table 3).

Immune dysfunction is one of the main risk factors for *Candida* infection. Therefore, the neutrophil granulocyte count and T cell count of patients at the time of suspected *Candida* infection were further analyzed. The $CD3^{+}$T cell counts (median=520/μl, IQR 396-710) and $CD4^{+}$ Th cell counts (median=284/μl, IQR 218-354) of patients diagnosed with candidemia

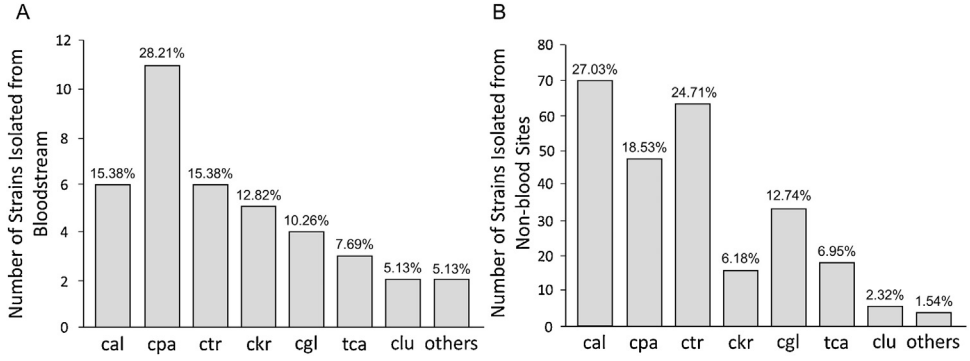

Fig. 1 – Strains of *Candida* spp. isolated from bloodstreams of 39 patients with candidemia (A), and form the non-blood body sites of 168 burn patients (22 with candidemia) (B). Abbreviations: cal – C.albicans, cpa – C.parapsilosis, cgl – C.glabrata, ckr – C. krusei, tca – C.famata, clu –C.lusitaniae.

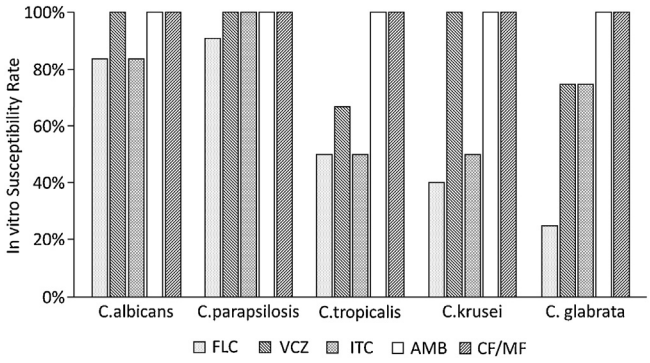

Fig. 2 – In vitro antifungal susceptibility of *Candida* strains isolated from bloodstream. Abbreviations: FLC– Fluconazole, VCZ– voriconazole, ITC– itraconazole, CF– caspofungin, MF– micafungin.

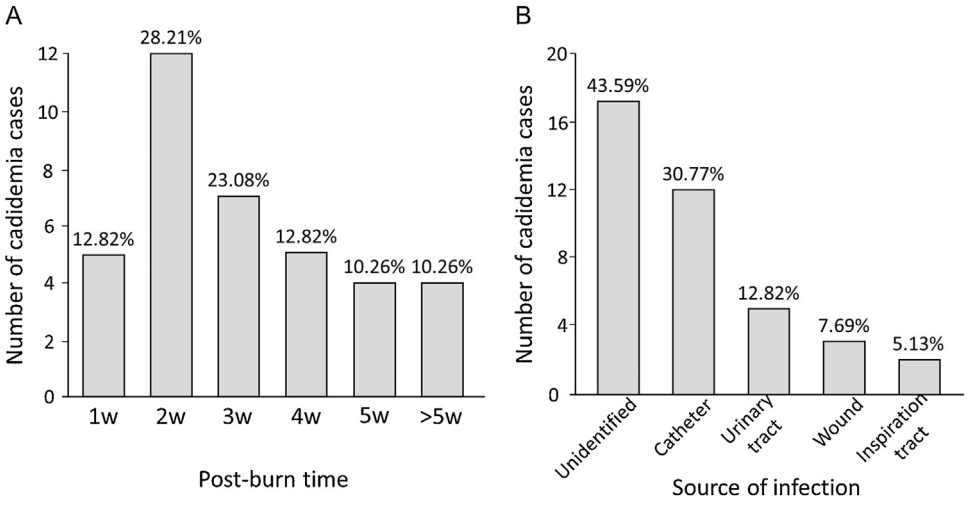

Fig. 3 – Time distribution of candidemia cases in various after burn weeks (A), and sources of the bloodstream *Candida* infection (B).

were significantly lower than those of patients without candidemia (median 692/μl, IQR 512-964 and median 344/μl, IQR 244-465, p=0.001 and 0.041, respectively), although both were lower than the limit of the normal reference value. For the $CD4^+/CD8^+$ ratio, no difference was observed between the two groups. The neutrophil granulocyte count, a commonly used indicator of cell immune function and a risk factor of opportunistic infection, showed no difference between patients with candidemia (median 11.25×10^9/L, IQR 6.76-14.55×10^9/L) and the controls (median 9.87×10^9/L, IQR 6.15-12.43×10^9/L) (Fig. 4A). And the neutrophil granulocyte counts of both groups were higher than the normal reference value (Fig. 4B).

Serological assays were widely used in the diagnosis of systemic *Candida* infection. In this study, 179 patients underwent (1-3)-β-D-glucan (BG) test for suspected *Candida* infection. For patients diagnosed with candidemia, 22 patients got positive results (≥60pg/ml) in the 1 week before the blood culture was performed. The sensitivity and specificity of the BG test for diagnosis of candidemia were 56.41% and 72.19%, respectively.

A total of 43.65% of major burn patients, mainly the patients with prior *Candida* colonization (83.44%), and 43.59% (17 cases) of candidemia cases received prophylactic antifungal drugs prior to the candidemia episodes. For patients diagnosed with candidemia, 64.7% had received azoles, and the others received echinocandins for prophylactic therapy. It was appropriate in 12 cases (70.59%) according to in vitro antifungal susceptibility test. Prophylactic administration of azoles was appropriate in only 54.55% of cases.

For targeted therapy after diagnosis of candidemia and susceptibility assays, azoles or echinocandins were administrated in 35.90% patients, respectively. The other 28.20% patients received combination antifungal therapy (azoles combined with amphotericin B, or azoles combined with echinocandins). The average duration of targeted antifungal treatment was 15.74±5.92 days.

In terms of prognosis, the mean lengths of ICU and total hospital stay for patients with candidemia were 39.03 ±24.51 and 81.94±53.17 days, respectively, significantly prolonged when compared to patients without candidemia (p=0.001 and 0.117, respectively). The overall mortality of the patients in the BICU was 9.76%. The mortality of patients suffering from candidemia was 23.08%, significantly higher than that of the patients without candidemia (8.36%, $p<0.001$).

Table 3 – Risk factors of candidemia, analyzed by multivariate logistic regression.

Risk factors	OR	95%CI	p Value
Sex (male)	2.87	1.01–7.32	NS
Age (years)	1.02	0.99–1.03	NS
Burn area	0.97	0.93–1.02	NS
Full thickness area	1.14	0.87–1.49	NS
Inhalation injury	2.06	1.23–5.46	0.02
Abbreviated burn severity index	1.46	0.96–2.24	NS
Tracheotomy	0.83	0.16–4.01	NS
Mechanical ventilation	1.67	0.83–3.39	NS
Central vascular catheter	1.03	0.21–5.13	NS
Parenteral nutrition	0.78	0.16–3.21	NS
Renal dysfunction need replacement	3.41	1.04–9.05	0.04
Gastrointestinal complications	4.97	1.46–17.06	0.01
Corticosteroids	0.77	0.11–4.06	NS
Hypotension	1.31	0.46–3.60	NS
Broad-spectrum antibacterial	1.01	0.21–5.01	NS
Diabetes	0.65	0.30–3.48	NS
T-cell lymphopenia	1.74	1.28–7.84	0.02
Prior Candida colonization	1.62	1.12–4.55	0.04
Prophylactic antifungal drugs	0.99	0.35–3.10	NS
Bacteremia	1.31	0.66–2.57	NS

NS: $p \geq 0.05$.

The mortality attributable to candidemia was 14.99% (95% CI=10.24%–19.74%).

4. Discussion

Candidemia remains an important cause of ICU sepsis, posing a particularly serious risk in burn patients. In our study, the overall incidence of candidemia was 9.51%, higher than the incidences described by some other authors [13]. TBSA and ABSI are indicators of severity of burn injury that have been described previously as predisposing factors for candidemia and invasive *Candida* infection, the variation in the incidence of candidemia might be attributable to the characteristics of patients across various studies. In present study, patients included had an average TBSA over 60%, and the average ABSI score was 6.31±2.54, making them a high-risk group for the development of invasive *Candida* infection. Moreover, there was an apparent upward tendency in the incidence of candidemia over the 6 years in our BICU. A rise in invasive *Candida* infection or candidemia incidences among burn patients has been observed in different burn centers worldwide [6]. The cause of this finding might be selection for fungal pathogen as a result of an increased early usage of broad-spectrum antibiotics [14]. Therefore, *Candida* infection represents an important emerging threat to the burn patients, and might suggest aggressive prevention among this group.

Although C.albicans plays a dominant role in candidemia in most previous studies, a worldwide trend toward the increasing isolation of non-albicans *Candida* spp. has been noticed [7,15-17]. In this study, the most common species isolated from the bloodstream was C.parapsilosis (28.21%), followed by C.tropicalis and C. albicans (15.38%, respectively). This is the first report regarding the dominance of non-albicans *Candida* spp. in burn patients, although it concerns a specific group with small sample size.

Due caution should be exercised because the non-albicans spp. had a remarkably higher resistance rate to antifungal agents [14]. Therefore, it is pivotal to know the susceptibility pattern in this particular population in order to initiate therapy with appropriate antifungal drugs prior to the completion of susceptibility tests. In our study, the isolated strains of C. glabrata and C.krusei showed high levels of resistance to FLC and itraconazole, in accordance with the previous reports [18]. However, C.tropicalis, reported as resistant only to FLC traditionally, also showed decreased susceptibility to all azoles, even including voriconazole. Considering the high resistance rate of C.tropicalis, and the high mortality rate associated with it, more aggressive antifungal therapy might be used in patients with C.tropicalis infections [14].

The overall resistance rate of *Candida* spp. to FLC was 35.89%, and the prophylactic administration of FLC was appropriate in only 54.55% cases of candidemia. This finding supported the reports of increasing isolates of non-albicans *Candida* spp. with promoted resistance to FLC among non-neutropenic candidemia patients over recent decades [19].

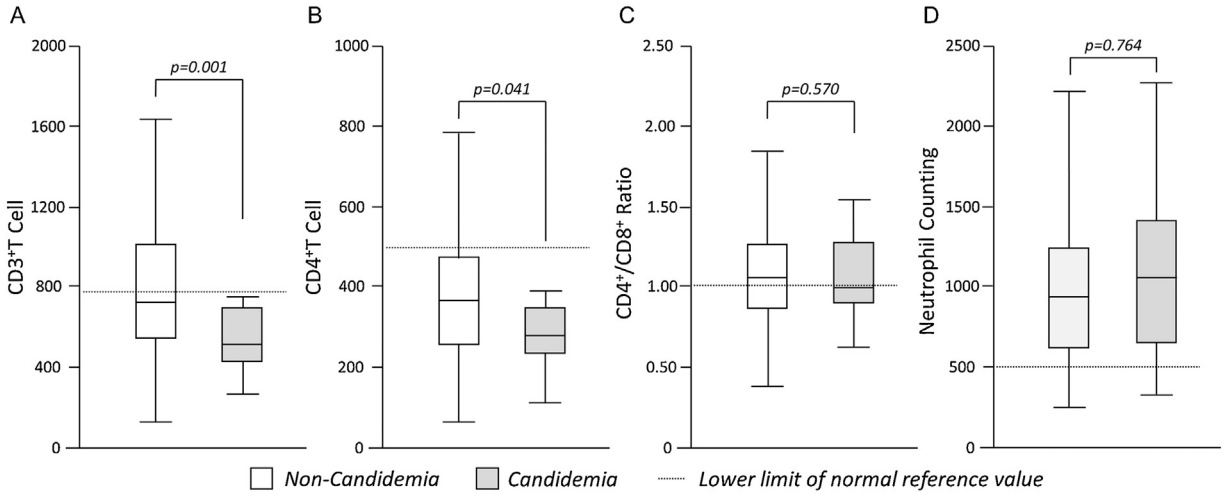

Fig. 4 – Peripheral blood lymphocyte counts (A) and neutrophil granulocyte counts (B) at the time of suspected bloodstream *Candida* infection patients who admitted from 2015 to 2017 (184 burn patients, with 21 cases of candidemia).

Similar to FLC, an increasing resistance rate to itraconazole was also observed in this study. We propose that the widely application of the two agents for antifungal therapy, especially for prophylaxis, is the potential reason. Voriconazole and had excellent in vitro activity against most *Candida* spp. except for C. tropicalis. We found no resistance to echinocandins (micafungin and caspofungin) or amphotericin B. Given the increasing resistance to antifungal agents, especially to fluconazole and itraconazole, echinocandins or voriconazole might be more effective for empirical therapy for candidemia in major burn patients.

In this study, most cases of candidemia were diagnosed in the second and third weeks of the after burn period (53.85%). This was in accordance with the results of previous studies about invasive candidiasis in burn patients [20,21]. During this period, the lysis of eschar and the beginning of *Candida* colonization increase the risk of invasive infection [6,22]. Therefore, precaution and prophylaxis practices against fungal infection should be taken for patients at high risk during this period [8].

Candida infection was associated with the severity of burn injury, including the burn size and the complications. Patients who suffered from candidemia commonly had a greater burn area than patients without candidemia [6]. Nevertheless, neither burn area nor ABSI score was identified as risk factor of candidemia in this study. A reason for this observation might be that the patients included in this study had more extensive burn areas (average TBSA=61.15±20.73%) compared to other studies, which made no difference in burn size between the two groups.

Although no difference was found in TBSA between the patients with candidemia and the controls, three complications of burn injury (inhalation injury, renal dysfunction with replacement therapy and gastrointestinal complications) were found to be important risk factors of candidemia. Approximately 10% of burn patients suffered from inhalation injury in our burn center [23]. Inhalation injury may lead to prolonged duration of mechanical ventilation and more and longer courses of antibacterial treatment, thereby increasing the risk of secondary fungal infections [24]. Gastrointestinal perforations and abdominal surgery have also been reported to be associated with invasive candidiasis [13]. In burn ICUs, abdominal visceral injuries following high-voltage electric burn injuries, and severe gastrointestinal bleeding caused by stress ulcer were the most severe gastrointestinal complications, which lead to increasing risk of complicated intra-abdominal infections [25]. This study also confirmed that renal dysfunction with replacement therapy as a risk factor of candidemia. In burn patients, acute renal dysfunction is commonly caused by the hypoxic-ischemic damage in the early stage of burn injury. The replacement therapy required additional vascular access, which may increase the risk of opportunistic infections [26]. Therefore, a close pathogenic surveillance and prophylactic antifungal therapy should be considered in this specific group of major burn patients with inhalation injury, renal dysfunction or severe gastrointestinal complications.

It is well known that previous colonization by fungi at the non-blood body sties precedes systemic *Candida* infection [10]. In this study, 56.41% cases were found with *Candida* colonization before the development of candidemia. The rate of agreement between species of *Candida* isolated in colonization samples and blood cultures was 81.82%. Prior *Candida* colonization was most frequently found at burn wounds. Nevertheless, only 7.69% cases of candidemia were found to be derived from burn wound. In accordance with other studies, the most common identified focus of candidemia was the indwelling catheters, although in nearly half of the cases this focus could not be identified [7,27]. Hence, close monitoring of the catheters and proper daily management should be undertaken for the major burn patients, and the catheters should be removed after diagnosis of candidemia whenever possible [19].

We observed a significantly lower T lymphocyte count among the candidemia patients. Although the reduction of blood T cell counting is commonly observed in burn patients, it is the first report about the association between T cell lymphopenia and post burn candidemia. T lymphocytes, especially $CD4^+$ Th cells, play an important role in the onset and maintenance of phagocyte-dependent immunity to fungal infection. Severe burn and trauma may lead to reduction of peripheral T lymphocytes by suppression of bone marrow function, and induction of the apoptosis of mature T lymphocytes, which could last for over two weeks after burn injury [28]. The post burn T cell lymphopenia coincided with the diagnosis of most candidemia cases, give a clue that it may play an important role in the development of invasive *Candida* infection [29]. Therefore, T lymphocyte counts could be indicators of the risk of systemic *Candida* infection in burn patients.

By contrast, we found no reduction of neutrophils among candidemia patients. It has been reported that neutrophils appear to be a major source of the directive cytokines that contribute to the selection of Th1 and Th2 cell responses in *Candida* infection, and neutropenic refer to high risk for developing candidemia [30]. While another study also reported elevation of neutrophils and monocytes after burn injury [31]. This may be associated with dysregulation of immunity and hyperinflammatory responses after burns.

Intervention factors in ICU, including the use of total parenteral nutrition, intubation with central venous catheters, mechanical ventilation and history of broad-spectrum antibiotics, which have traditionally been reported to be associated with invasive *Candida* infection, were not found to be risk factors for candidemia in this study [7,32]. This finding might be attributed to the ubiquity of these medical interventions in major burn patients in this study. A further study including burn patients with lesser severity may help a better identification of high risk patients in burn ward.

Because the low positive rate and time lag of fungus cultures may possibly lead to delay of therapy, serological assays including BG test were commonly used as indicators of invasive *Candida* infection [33]. Nevertheless, the significance of BG test in burn fungal infection is still controversial as it was reported that the serum BG level was correlated with the severity of burn injury, and the exposure to gauze may also lead to false-positive BG assays [34]. In this study, we found that the BG test showed a low sensitivity (56.41%) but moderate specificity (72.19%) in the diagnosis of candidemia. However, the sensitivity of BG test might be underestimated because of

the high rate of missed diagnosis of candidemia in clinic [33]. Therefore, further studies are needed to clarify the utility of BG test in diagnosis of invasive *Candida* infection and guidance of empirical antifungal treatment in burn patients.

The overall mortality of major burn patients was 9.76%, and the mortality attributable to candidemia was 14.99% in this study. This finding was in accordance with the finding of Fochtmann's report, although the percentage was lower than that shown in most other similar publications [6,7,15]. It is reported that the mortality of candidemia was associated with the delay in starting candidemia treatment, the relatively lower mortality in our study might be related to the extensive administration of prophylactic antifungal therapy in patients at high risk for candidemia [21,35]. Nevertheless, this hypothesis was not proven in our study because of its retrospective character and the limited number of cases.

Our study has several limitations. Because of the limited number of major burn patients and the relatively low incidence of candidemia, this was a retrospective study. The T lymphocyte assay was not available in our burn center until 2015. That means some data of patients, were not acquired in this study. Furthermore, the risk factors associated with mortality were not analyzed because of the limited size of the sample. A prospective cohort study may provide a better understanding of candidemia in major burn patients.

5. Conclusion

Candidemia has a high incidence and mortality in major burn patients. Inhalation injury, renal dysfunction with replacement therapy, gastrointestinal complications, T-cell lymphopenia and prior *Candida* colonization were identified as risk factors for candidemia in the BICU. The changes in etiology and drug sensitivity, especially the increasing isolation of non-albicans *Candida* strains with reduced susceptibility to azoles represent new challenges for the management of candidemia in BICUs.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

There is no conflict of interest. And this work was supported by Chinese NSFC grants (81772088) to Junyi Zhou.

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