Epidemiology, Species Distribution, and Outcome of Nosocomial Candida spp. Bloodstream Infection in Shanghai — An 11-year Retrospective Analysis in a Tertiary Care Hospital

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Research Article

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Abstract

Background

The incidence of *Candida* bloodstream infections (BSIs), has increased over time. In this study, we aimed to describe the current epidemiology of *Candida* BSI in a large tertiary care hospital in Shanghai and to determine the risk factors of 28-day mortality and the impact of antifungal therapy on clinical outcomes.

Methods

All consecutive adult inpatients with *Candida* BSI at Ruijin Hospital from 2008.1 to 2018.12 were enrolled. Underlying diseases, clinical severity, species distribution, antifungal therapy, and their impact on the outcomes were analyzed.

Results

Among the 370 inpatients with 393 consecutive episodes of *Candida* BSI, the incidence of nosocomial *Candida* BSI was 0.39 episodes/1000 hospitalized patients. Of the 393 cases, 299 (76.1%) were treated with antifungal therapy (247 and 52 were treated with early appropriate and targeted antifungal therapy, respectively). The overall 28-day mortality rate was 28.5%, which was significantly lower in those who received early appropriate (25.5%) or targeted (23.1%) antifungal therapy than in those who did not (39.4%; P=0.012 and P=0.046, respectively). In multivariate Cox regression analysis, age, chronic renal failure, mechanical ventilation, and neutropenia were found to be independent risk factors of 28-day mortality rate. Patients who received antifungal therapy had a lower mortality risk than did those who did not.

Conclusions

The incidence of *Candida* BSI has increased steadily in the past 11 years at our tertiary care hospital in Shanghai. Antifungal therapy influenced short-term survival, but no significant difference in mortality was observed between those who received early appropriate and targeted antifungal therapy.

1. Background

The incidence of invasive fungal infection has increased over time, especially for *Candida* bloodstream infections (BSIs), which is associated with considerable excess mortality and costs [1-3]. In the past two decades, the incidence of fungal infection has increased from 0.1 episodes/1000 admissions to 0.3-0.6 episodes/1000 admissions in China, North America, and some European countries [4-7]. The mortality rate ranges from 35%-53% [8-11]. The optimal management of *Candida* BSIs included early awareness of patients at risk, control of the infection source, and timely administration of appropriate antifungal agents [12, 13]. Consequently, antifungal agents have been widely used as empirical therapy. However, the overuse of antifungal agents results in increased costs, toxicity, and ecological selection pressure for antifungal resistance and adverse drug interactions. Several studies showed that delayed antifungal therapy (more than 48h from onset) is associated with higher mortality [14], whereas others have reported conflicting results [15-17].

In this study, we retrospectively analyzed data from all patients with *Candida* BSI at our hospital between 2008 and 2018, aiming to describe their clinical characteristics, species distribution, antifungal therapy and to determine the risk factors for 28-day mortality.

2. Methods

2.1 Study setting and population

A retrospective analysis of data on consecutive Candida BSI episodes in adult inpatients (≥18 years) between January 1, 2008 and December 31, 2018, collected from the microbiology database of a 1900-bed teaching hospital in Shanghai, was performed.

Demographics and data on underlying diseases, comorbidities, severity of clinical features, Candida species distribution, and early appropriate or targeted antifungal treatment were compared among the patients with *Candida* BSI. Data on the initial and targeted antifungal agents used were also collected.

Candida BSI was defined as at least one positive blood culture for Candida. [18]. Neutropenia was defined as <500/mm³ absolute neutrophil count. Prior corticosteroid was defined as receiving >1 mg/kg/d prednisone for more than one week or equivalent before Candida BSI onset.

2.2 Laboratory methods

Isolates were detected from blood cultures using the BACTEC™ FX system (Becton Dickinson, Inc., Sparks, MD, USA), identified using matrix-assisted laser desorption ionization-time of flight mass spectrometer (bioMérieux, Marcy-l’Etoile, France). Susceptibility testing for flucytosine, amphotericin B,
fluconazole, voriconazole, and itraconazole was performed using the ATB® FUNGUS 3 system (BioMérieux, France), which is widely used in China [19]. This test provides information on susceptibility to antifungal agents, which is concordant with that obtained using the methodologies of the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) [20].

Early appropriate antifungal treatment was defined as commencement of appropriate drug treatment at an adequate dosage before obtaining in vitro susceptibility test results. The adequate dosage of the antifungal agent was defined according to 2009 or 2016 Infectious Diseases Society of America (IDSA) guidelines [18, 21]. Targeted antifungal treatment was defined as commencement of appropriate targeted treatment after obtaining results from susceptibility testing, regardless of whether the antifungal treatment initiated was appropriate. Crude mortality was calculated from data on deaths registered 28 days after the occurrence of Candida BSI.

2.3 Statistical analysis

Descriptive and subgroup analyses were performed for the baseline characteristics, and continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range according to their distributions. The chi-square test or 2-tailed Fisher exact test was applied to categorical variables. To identify the risk factors for 28-day mortality, multivariate Cox regression analysis was performed, and adjusted hazard ratio (HRs) with 95% confidence intervals (CIs) were reported. Variables that were associated with 28-day mortality in the Cox univariate analyses with a P<0.05 were entered into the multivariate Cox regression analysis model based on the forward selection. Two-tailed tests of significance at the level of a P value <0.05 level was considered as significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y. USA).

2.4 Ethics

The study was approved by Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine institutional review board, and written informed consent was not required because of the observational nature of this study.

3. Results

3.1 Incidence and clinical features of Candida BSI episodes

Data on a total of 393 consecutive episodes of Candida BSI were collected from 370 inpatients during the 11-year study period. The demographic characteristics of the patients are summarized in Table 1. The mean age of the patients was 57.6±19.0 years, and 74.3% were male. Candida BSI incidence was 0.39 episodes/1000 admissions. The incidence increased steadily from 0.21 (2008), to 0.59 (2017), to 0.33 episodes per 1,000 admissions (2018) (Figure 1[A]). Among the 393 Candida BSI episodes, 148 (37.7%), 167 (42.5%), and 78 (19.8%) occurred in the surgical ward, intensive care units (ICUs), and internal medicine ward, respectively (Figure 1[B]).

C. albicans was isolated in 19.3%, 41.2% and 38.9%, of cases in internal medicine wards, surgery wards, and the ICU, respectively (P=0.003). A higher proportion of C. tropicalis (34.7%) was found in internal medicine wards than in the surgery wards (21.6%) and ICUs (21.6%).

Most patients with Candida BSI had at least one comorbidity. These included 118 (30%) with solid tumors, 48 (12.2%) had hematological malignancies, 77 (19.6%) had diabetes mellitus, 124 (31.6%) had chronic cardiac disease, 52 (13.2%) had chronic pulmonary disease, 42 (10.7%) had chronic renal failure, in 26 (6.6%) patients, the skin barrier was considered compromised, 244 (62.1%) had prior surgical intervention, 54 (13.7%) used corticosteroid, 88 (22.4%) used prior antifungal agents, and 255 (64.9%) received antibiotics prior Candida BSI onset. A total of 244 (72%) patients had at least two comorbidities. No patient had human immunodeficiency virus (HIV) infection. Regarding the severity, 309 (78.6%) had fever, 180 (45.8%) received parenteral nutrition, 147 (37.4%) received mechanical ventilation, 49 (12.5%) received renal replacement therapy, and 42 (10.7%) had neutropenia. The clinical characteristics of patients by Candida species are shown in Table 1.
Table 1
Demographic and clinical data for patients with *Candida* bloodstream infection

|                | *C. albicans* (n=141) | *C. parapsilosis* (n=87) | *C. tropicalis* (n=69) | *C. glabrata* (n=48) | *C. guilliermondii* (n=20) | *C. sake* (n=8) | *C. krusei* (n=5) | Other *Candida* spp. (n=15) | Total (n=393) |
|----------------|------------------------|--------------------------|-----------------------|-----------------------|---------------------------|-----------------|------------------|-------------------------|-----------------|
| Age, y         | 65.2±14.5              | 53.2±20.3                | 50.5±19.5             | 60.7±17.5             | 50.5±19.4                 | 52±20.6         | 40.8±27.1        | 52.6±20.0               | 57.6±19.0       |
| Male           | 102(73.4)              | 60(69.0)                 | 51(73.9)              | 44(91.7)              | 14(70)                    | 8(100)          | 2(40)            | 11(73.3)                | 292(74.3)       |
| Origin         | Internal medicine ward | 15(10.6)                 | 19(21.8)              | 27(39.1)              | 7(14.6)                   | 3(15)           | 0(0)             | 3(26.7)                 | 78(19.8)        |
| Surgical ward  | 61(43.3)               | 32(36.8)                 | 16(23.2)              | 15(31.3)              | 10(50)                    | 6(75)           | 0(0)             | 8(53.3)                 | 148(37.7)       |
| ICU            | 65(46.1)               | 36(41.4)                 | 26(37.7)              | 26(54.1)              | 7(35)                     | 2(25)           | 2(40)            | 3(20)                   | 167(42.5)       |
| Time from admission to infection, d | 30.6±35.3 | 48.4±56.2 | 37.7±32.4 | 27.5±19.1 | 35.9±52.5 | 120.6±242.7 | 64.2±68.6 | 21.5±13.6 | 37.6±53.1 |
| Length of hospital stay, d | 56.0±54.9 | 83.2±78.1 | 71.5±56.1 | 67.1±72.7 | 97.7±142.6 | 178.5±281.7 | 92.4±88.5 | 52.7±101.5 | 71.1±82.8 |
| Turnaround Time, d | 4.3±1.9 | 4.5±1.1 | 3.8±1.1 | 4.8±1.3 | 4.3±1.2 | 4.5±1.6 | 4.4±1.5 | 5.9±1.8 | 4.4±1.5 |
| Underlying disease | Solid tumor | 47(33.3) | 26(29.9) | 13(18.8) | 17(35.4) | 6(30) | 2(25) | 0(0) | 7(46.7) | 118(30) |
|                | Hematologic malignancy | 8(5.7) | 6(6.9) | 24(34.8) | 2(4.2) | 2(10) | 1(12.5) | 3(60) | 2(13.3) | 48(12.2) |
|                | Diabetes mellitus | 33(23.4) | 21(24.1) | 8(11.6) | 9(18.8) | 1(5) | 1(12.5) | 0(0) | 4(26.7) | 77(19.6) |
|                | Chronic cardiac disease | 55(39) | 22(25.3) | 16(23.2) | 18(37.5) | 6(30) | 3(37.5) | 2(40) | 2(13.3) | 124(31.6) |
|                | Chronic pulmonary disease | 26(18.4) | 9(10.3) | 5(7.2) | 6(12.5) | 1(5) | 1(12.5) | 1(20) | 3(20) | 52(13.2) |
|                | Chronic renal failure | 18(12.8) | 6(6.9) | 6(8.7) | 5(10.4) | 5(25) | 0(0) | 0(0) | 2(13.3) | 42(10.7) |
|                | Skin barrier compromised | 5(3.5) | 9(10.3) | 5(7.2) | 1(2.1) | 3(15) | 3(37.5) | 0(0) | 0(0) | 26(6.6) |
|                | Prior surgical intervention (<1 month) | 97(68.8) | 48(55.2) | 36(52.2) | 30(62.5) | 15(75) | 6(75) | 2(40) | 10(66.7) | 244(62.1) |
| Corticosteroid use | 11(7.8) | 13(14.9) | 12(17.4) | 9(18.8) | 4(20) | 0(0) | 3(60) | 2(13.3) | 54(13.7) |
| Prior use of antifungal agents (<6 months) | 20(14.2) | 19(21.8) | 24(34.8) | 11(22.9) | 8(40) | 1(12.5) | 4(80) | 1(6.7) | 88(22.4) |
| Severity of clinical feature | Fever (T>38.2°C) | 114(80.9) | 63(72.4) | 60(87) | 34(70.8) | 16(80) | 6(75) | 3(60) | 13(86.7) | 309(78.6) |
|                | Parenteral nutrition | 71(50.4) | 42(48.3) | 28(40.6) | 23(47.9) | 5(25) | 3(37.5) | 2(40) | 6(40) | 180(45.8) |
|                | Mechanical ventilation | 58(41.1) | 31(35.6) | 23(33.3) | 25(52.1) | 5(25) | 2(25) | 2(40) | 1(6.7) | 147(37.4) |
| Renal replacement therapy | 17(12.1) | 10(11.5) | 9(13) | 7(14.6) | 5(25) | 0(0) | 1(20) | 0(0) | 49(12.5) |
|--------------------------|----------|----------|-------|---------|-------|------|-------|------|---------|
| Central venous catheter  | 121(85.8) | 67(77) | 49(71) | 43(89.6) | 17(85) | 5(62.5) | 4(80) | 10(66.7) | 316(80.4) |
| Neutropenia              | 4(2.8) | 8(9.2) | 22(31.9) | 1(2.1) | 2(10) | 0(0) | 3(60) | 2(13.3) | 42(10.7) |
| 28-day mortality         | 54(38.3) | 16(18.4) | 19(27.5) | 13(27.1) | 3(15) | 1(12.5) | 1(20) | 5(33.3) | 112(28.5) |

Other *Candida* spp. Includes *C. gum* (4 cases), *C. lusitaniae* (3 cases), *C. intermedia* (2 cases), *C. lipolecta* (2 cases), *C. theae* (2 cases), *C. famata* (1 case), and *C. haemulonii* (1 case).

Data were expressed as mean ± SD for continuous variables and n (%) for categorical variables. ICU, intensive care unit; SD, standard deviation

### 3.2 Antifungal susceptibility of *Candida* isolates

A total of 393 *Candida* spp. were isolated, including 141 (35.9%), *C. albicans*, 87, *C. parapsilosis* (22.1%); 69, *C. tropicalis* (17.6%); 48, *C. glabrata* (12.2%); 20, *C. guilliermondii* (5.1%); 8, *C. sake* (2.0%); 5, *C. krusei* (1.3%); and 15, other species (4, *C. gum*; 3, *C. lusitaniae*; 2, *C. intermedia*; 2, *C. theae*; 2, *C. lipolecta*; 1, *C. famata*; and 1, *C. haemulonii*).

Among the 393 *Candida* species, 378 were subjected to antifungal susceptibility testing, on the basis of 2012 CLSI breakpoints (CBPs). As shown in Table 2, the susceptibility of *C. albicans*, *C. parapsilosis* to fluconazole and voriconazole were quite high, compared to that to itraconazole (94%, 93.3% vs. 82.1%). The susceptibility of *C. tropicalis* to triazoles fluconazole, voriconazole, and itraconazole was unsatisfactory. Amphotericin B and 5-flucytosine remained superior against common Candida spp., except for *C. krusei* and *C. guilliermondii*, with 95% susceptibility.
Table 2

Antifungal susceptibility testing results (ATB Fungus 3) of 378 Candida [n (%)]

|                      | C.albicans (n=134) | C.parapsilosis (n=86) | C.tropicalis (n=67) | C.glabrata (n=47) | C.krusei (n=5) | C.sake (n=8) | C.guilliermondii (n=19) | Other Candida spp. (n=12) | Total (n=378) |
|----------------------|--------------------|-----------------------|--------------------|-------------------|----------------|-------------|-----------------------|---------------------------|------------------|
| Fluconazole          |                    |                       |                    |                   |                |             |                       |                           |                  |
| S                    | 126 (94)           | 77 (89.5)             | 35 (52.2)          | 0 (0)             | 8 (100)        | 13 (68.4)   | 9 (75.0)              |                           | 268 (70.9)      |
| SDD                  | 1 (0.8)            | 6 (7.0)               | 3 (4.5)            | 44 (93.6)         | 0 (0)          | 0 (0)       | 0 (0)                 |                           | 54 (14.3)       |
| R                    | 7 (5.2)            | 3 (3.5)               | 29 (43.3)          | 3 (6.4)           | 5 (100)        | 6 (31.6)    | 3 (25.0)              |                           | 56 (14.8)       |
| Itraconazole         |                    |                       |                    |                   |                |             |                       |                           |                  |
| S                    | 110 (82.1)         | 75 (87.2)             | 25 (37.3)          | 0 (0)             | 8 (100)        | 6 (31.6)    | 9 (75.0)              |                           | 233 (61.6)      |
| SDD                  | 6 (4.5)            | 7 (8.1)               | 4 (6.0)            | 40 (85.1)         | 2 (40.0)       | 7 (36.8)    | 0 (0)                 |                           | 66 (17.5)       |
| R                    | 18 (13.4)          | 4 (4.4)               | 38 (56.7)          | 7 (14.9)          | 3 (60.0)       | 6 (31.6)    | 3 (25.0)              |                           | 79 (20.9)       |
| Voriconazole         |                    |                       |                    |                   |                |             |                       |                           |                  |
| S                    | 125 (93.3)         | 79 (91.9)             | 41 (61.2)          | 45 (95.8)         | 8 (100)        | 12 (63.2)   | 11 (91.7)             |                           | 325 (86.0)      |
| SDD                  | 0 (0)              | 2 (2.3)               | 2 (3.0)            | 1 (2.1)           | 1 (2.0)        | 3 (15.8)    | 0 (0)                 |                           | 9 (2.4)         |
| R                    | 9 (6.7)            | 5 (5.8)               | 24 (35.8)          | 1 (2.1)           | 0 (0)          | 4 (21.0)    | 1 (8.3)               |                           | 44 (11.6)       |
| Amphotericin B       |                    |                       |                    |                   |                |             |                       |                           |                  |
| S                    | 133 (99.3)         | 83 (96.5)             | 67 (100)           | 47 (100)          | 5 (100)        | 18 (94.7)   | 11 (91.7)             |                           | 372 (98.4)      |
| R                    | 1 (0.7)            | 3 (3.5)               | 0 (0)              | 0 (0)             | 0 (0)          | 1 (5.3)     | 1 (8.3)               |                           | 6 (1.6)         |
| Flucytosine          |                    |                       |                    |                   |                |             |                       |                           |                  |
| S                    | 132 (98.5)         | 85 (98.8)             | 65 (97.0)          | 46 (97.9)         | 1 (20.0)       | 8 (100)     | 9 (47.4)              | 12 (100)        | 358 (94.7)      |
| R                    | 2 (1.5)            | 1 (1.2)               | 2 (3.0)            | 1 (2.1)           | 4 (80.0)       | 0 (0)       | 10 (52.6)             | 0 (0)           | 205 (53.3)      |

15 Candida spp. isolates did not have a susceptibility test, C. albicans (7), C. parapsilosis (2), C. tropicalis (2), and glabrata, theae, gum, haemulonii each.

R, resistance; S, susceptible; SDD, susceptible dose dependence.

3.3 Antifungal therapy and outcome of patients with Candida BSI

Antifungal therapy was administered to 299 (76.1%) patients, whereas 94 (23.9%) patients did not receive antifungal therapy. Among those who received antifungal therapy, 247 (62.8%) received early appropriate antifungal therapy, and 52 (13.2%) received targeted antifungal therapy. Fluconazole was most frequently used as an empirical therapy, followed by echinocandins and voriconazole. Eighteen (4.6%) patients with Candida BSI received combination therapy.

The overall, 28-day mortality rate was 28.5%, and the rate was significantly higher in internal medicine wards and ICUs than in surgical wards (37.2% and 34.7% vs. 16.9%, respectively, P<0.001). The mortality rates among those who received early appropriate or targeted antifungal therapy was 26.8% and 25.1% (P=0.012 or P=0.046), compared to 39.3% for those who did not receive any antifungal therapy, with no significant difference between those who received early appropriate antifungal therapy and those who received targeted antifungal therapy.
On univariate analysis, age, solid tumor, diabetes mellitus, chronic cardiac disease, chronic renal failure, skin disease, prior surgical intervention, mechanical ventilation, neutropenia, and antifungal therapy were found to be associated with 28-day mortality. On multivariate Cox regression analysis, advanced age (HR=1.025; 95%CI, 1.013-1.037; P<0.001), chronic renal failure (HR=2.018; 95%CI 1.234-3.299; P=0.005), mechanical ventilation (HR=1.950; 95%CI 1.307-2.912; P=0.001), and neutropenia (HR=4.347; 95%CI 2.462-7.675; P<0.001), were found to be independent risk factors for 28-day mortality. However, antifungal therapy (HR=0.570; 95%CI 0.382-0.849; P=0.006) was an independent protective factor for 28-day mortality (Table 3).

### Table 3

Multivariable Cox regression analysis for 393 Candida bloodstream infection episodes

| 28-day outcome | Multivariable analysis |
|---------------|------------------------|
| Survival (n=281) | Death (n=112) | P-value | HR (95%CI) | P-value |
| Male | 216(76.9) | 76(67.9) | 0.065 | - | - |
| Age, y | 55.2(19.5) | 63.6(16.2) | <0.01 | 1.025(1.013-1.037) | <0.001 |
| Underlying disease | - | - | - | - |
| Solid tumor | 91(32.4) | 27(24.1) | 0.106 | - | - |
| Hematologic malignancy | 32(11.4) | 16(14.3) | 0.428 | - | - |
| Diabetes mellitus | 49(17.4) | 28(25) | 0.088 | - | - |
| Chronic Cardiac disease | 72(25.6) | 52(46.4) | <0.01 | - | 0.105 |
| Chronic Pulmonary disease | 34(12.1) | 18(16.1) | 0.294 | - | - |
| Chronic renal failure | 20(7.1) | 22(19.6) | <0.01 | 2.018(1.234-3.299) | 0.005 |
| Skin barrier compromised | 24(8.5) | 2(1.8) | 0.015 | - | 0.308 |
| Prior surgical intervention (<1month) | 182(64.8) | 62(55.4) | 0.083 | - | - |
| Corticosteroid use | 40(14.2) | 14(12.5) | 0.652 | - | - |
| Prior antifungal agents use (<6month) | 64(22.8) | 24(21.4) | 0.772 | - | - |
| **Severity of clinical feature** | - | - | - | - |
| Fever (T>38.2°C) | 220(78.3) | 89(79.5) | 0.798 | - | - |
| Parenteral nutrition | 124(44.1) | 56(50) | 0.292 | - | - |
| Mechanical ventilation | 89(31.7) | 58(51.8) | <0.01 | 1.950(1.307-2.912) | 0.001 |
| Renal replacement therapy | 32(11.4) | 17(15.2) | 0.305 | - | - |
| Central venous catheter | 227(80.8) | 89(79.5) | 0.766 | - | - |
| Neutropenia | 24(8.5) | 18(16.1) | 0.029 | 4.347(2.462-7.675) | <0.001 |
| Antifungal therapy | 224(74.9) | 75(25.1) | 0.007 | 0.502(0.294-0.857) | 0.006 |
| **No treatment** | 57(60.6) | 37(39.4) | - | - |

Data were expressed as mean ± SD for continuous variables and n (%) for categorical variables. SD, standard deviation.

### 4. Discussion

Our study showed that the incidence of Candida BSI has increased steadily in the past 11 years at our tertiary care hospital in Shanghai. Several studies have shown a substantial increase in Candida BSI incidence in the past two decades, which is similar to our study findings [4, 11, 22]. Intensive use of broad-spectrum antibiotics may be the main cause. In addition, gradually worsening hospitalized patient profiles, underlying comorbidities including malignancy, and a high frequency of surgeries may be predisposing risk factors for increased incidence.

C. albicans remains the most common pathogen causing Candida BSI. However, over the past two decades, an increased percentage of common non-C. albicans Candida spp. have been reported worldwide. In our study, non-C. albicans accounted for 64.1%. C. parapsilosis, C. tropicalis and C.
**declarations**

SD, standard deviation

**susceptibility testing; HR, hazard ratio; HIV, human immunodeficiency virus; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; BSI, bloodstream infection; CI, confidence interval; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HR, hazard ratio; HIV, human immunodeficiency virus; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; SD, standard deviation**

**5. conclusions**

Our retrospective study findings showed increased incidence of *Candida* BSI in the past 11 years in Shanghai. Although the percentage of non-*C. albicans* spp. has been increasing, *C. albicans* spp. remains the most frequently isolated species. The mortality of patients with *Candida* BSI was quite high, especially in internal medicine wards. Antifungal therapy improved the short-term survival of patients with *Candida* BSI. Whether preemptive antifungal therapy should be initiated or antifungal therapy should be initiated after the antifungal susceptibility test needs further discussion.

**Abbreviations**

BSI, bloodstream infection; CI, confidence interval; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HR, hazard ratio; HIV, human immunodeficiency virus; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; SD, standard deviation
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Competing Interests:
The authors declare that they have no competing interests.

Availability of data and materials:
All data generated or analyzed during this study are included in this published article.

Code availability:
Not applicable

Authors' contributions:
ZTY, EZC, and EQM made substantial contributions to conception and design. ZTY, LZH,YJZ, LW, TX LZ, and XYL participated in the acquisition of data. ZTY, YJZ, and YC drafted the manuscript. ZTY and EZC revised it critically.

Ethics Approval:
The study was approved by the local institutional review board (Ruijin Hospital, Shanghai Jiao Tong University, School of medicine).

Consent to participate:
Not applicable

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**Figures**

A) Distribution of Candida spp. and episodes/1000 admissions during the study period. Fig.1(B) Distribution of Candida spp. according to hospital wards; 148 episodes were from surgical wards, 167 episodes were from ICUs and 78 episodes were from the internal medicine wards.