Epidemiology, species distribution, and outcome of nosocomial Candida spp. bloodstream infection in Shanghai — A retrospective of 11-year clinical analysis in a shanghai tertiary hospital

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Research

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Abstract

Background:

Candida spp. are important opportunist pathogens causing bloodstream infections (BSIs). The present study aims to describe the current epidemiology of *Candida* BSI in a large Shanghai Tertiary-care Hospital from 2008 to 2018 and to identify the risk factors and the impact of antifungal therapy on clinical outcomes.

Methods:

From January 2008 to December 2018, all consecutive patients who developed *Candida* BSI at Ruijin Hospital were enrolled. Underlying diseases, clinical severity, species distribution, antifungal therapy, and its impact on the outcome were analyzed.

Results:

The incidence of nosocomial *Candida* BSI was 0.39 episodes/1000 hospitalized patients, and the overall 28-day mortality rate was 28.5%. Among the 393 cases of *Candida* BSI, 299 cases (76.1%) received antifungal therapy. 247 received early appropriate antifungal therapy (an appropriate drug with adequate dosage was started before the subsequent in vitro susceptibility results), and 52 received target antifungal therapy (appropriate target treatment started after susceptibility results, regardless of whether the inappropriate antifungal treatment has been initialed or not). The 28-day mortality rate was significantly lower in those who received early appropriate antifungal therapy or target antifungal therapy compared with those who did not receive antifungal therapy (25.5% and 23.1% vs. 39.4%,P = 0.012 and P = 0.046). In multivariate Cox regression analysis, age, chronic renal failure, mechanical ventilation, neutropenia were independent risk factors for the 28-day mortality rate, while antifungal therapy was a protective factor for short-term survival rate.

Conclusions:

The epidemiology of *Candida* BSI in Shanghai differed from that observed in Western countries. Antifungal therapy did influence the short-term survival, while there was no significant difference between the mortality for those who received early appropriate antifungal therapy and for those who received target antifungal therapy.

Background

The incidence of invasive fungal infection has increased over time, especially for *Candida* bloodstream infections (BSIs), which was associated with considerable excess mortality and costs. 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[1–4]. The mortality rate is ranging from 35%-53% [5–8]. 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. Consequently, antifungal agents have been widely used as empirical therapy. While the overuse of antifungal agents resulted in increased costs, toxicity, ecological selection pressure for antifungal resistance and adverse drug interactions, etc. Several studies showed that delayed antifungal therapy (more than 48 h from onset) was associated with higher mortality[9], while others have yielded conflicting results[10–12].

In this study, we retrospectively analyzed all *Candida* bloodstream infection patients from 2008 to 2018 in our hospital, aiming to describe their clinical characteristics, species distribution, antifungal therapy and to identify its risk factors for 28-day mortality.

Methods

Study Setting and population

A retrospective analysis of consecutive Candida bloodstream episodes in adults collected from the microbiology database of a 1900-bed teaching hospital in Shanghai was performed over 11 years (from 1st January 2008 to 31st December 2018).

Demographics, underlying diseases, co-morbidities, the severity of clinical features, Candida species distribution, and early appropriate or target treatment were compared among the patients with *Candida* BSI. The initial and target antifungal agent use was also collected.

A case of Candida BSI was defined as a patient with at least one blood culture positive for a Candida. [13]. Neutropenia was defined as <500/mm^3 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.

Laboratory Methods

Isolates were detected from blood cultures using the BACTEC^{TM} FX system (Becton Dickinson, Inc., Sparks, MD, USA). Flucytosine, amphotericin B, fluconazole, voriconazole, and itraconazole susceptibility testings were performed using the ATB® FUNGUS 3 system (BioMérieux, France), which was wildly used in China[14], providing susceptibility to antifungals results markedly concordant with those obtained using CLSI and EUCAST methodologies[15].

Early appropriate antifungal treatment was considered when the appropriate drug with adequate dosage was started before the subsequent in vitro susceptibility results. Adequate dosage of the antifungal agent was defined according to IDSA 2009 guidelines or 2016 IDSA[13, 16]. Target antifungal treatment was defined when appropriate target treatment started after susceptibility results, regardless of whether an inappropriate antifungal treatment has been initiated or not. Crude mortality was registered after 28 days from the occurrence of Candida BSI.

Statistical analysis

Descriptive analyses were used for baseline characteristics and subgroup analyses. Continuous variables were expressed as mean ± standard deviation (SD). The Chi-square-test or 2-tailed Fisher Exact-test was applied to categorical variables. To define risk factors for mortality, multivariate Cox regression analysis, and adjusted hazard ratio (HR) with 95% confidence interval (CI) were calculated. Variables that were associated with 28-day mortality in Cox univariate analyses with a $P<0.05$ were entered into multivariate cox analysis, based on the forward regression,2-tailed tests of significance at the level of a P value of <0.05 level was used to determine statistical significance. Statistical analysis has been performed with SPSS 22.0.

Ethics

The study was approved by the local institutional review board (Ruijin Hospital, Shanghai Jiaotong University, School of medicine) and written patient consent was not required because of the observational nature of this study.

Results

Incidence and demographic characteristics of patients

A total of 393 consecutive episodes of *Candida* BSI were collected, occurred among 370 inpatients, during an 11-year study period with an incidence of 0.39 episodes/1000 admissions, which has increased steadily, from 0.21 episodes per 1,000 admissions in 2008 to 0.59 in 2017 and 0.33 in 2018, as shown in Fig. 1. The demographic characteristics of the patients are summarized in Table 1. The mean age of patients was 57.6 ± 19.0 years and 74.3% were male. Among 393 episodes, 148 episodes (37.7%) were from the surgical ward, 167 episodes (42.5%) were from intensive care units (ICUs) and 78 episodes (19.8%) were from the internal medicine ward, as shown in Fig. 2.

Table 1
Demographic of patients with *Candida* bloodstream infection and distribution of *Candida species*

	C. albicans	*C. parapsilosis*	*C. tropicalis*	*C. glabrata*	*C. guilliermondii*	*C.sake*	*C.krusei*	Other *Candida spp.*	Total
	(n = 141)	(n = 87)	(n = 69)	(n = 48)	(n = 20)	(n = 8)	(n = 5)	(n = 15)	(n = 393)
Age (year)	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 [n (%)]	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 [n (%)]									
Internal medicine ward	15(10.6)	19(21.8)	27(39.1)	7(14.6)	3(15)	0(0)	3(60)	4(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
Other *Candida spp.* Includes *C. gum* (4 cases), *C. lusitaniae* (3 cases), *C. intermedia* (2 cases), *C. lipolytica* (2cases), *C. theae* (2 cases), *C.famata* (1case) and *C. haemulonii* (1 case).									
Abbreviation: ICU, intensive care unit									

Table 1 here

C. albicans was isolated in 19.3% of cases in internal medicine wards while in 41.2% and 38.9% of cases in surgery wards and ICU, respectively (P = 0.003). In contrast, a higher proportion of *C. tropicalis* (34.7%) was found in internal medicine wards compared to that in surgery wards (21.6%) and ICUs (21.6%).

Underlying Diseases And Clinical Features

The majority of patients with *Candida* BSI had at least one co-morbidity. 118 (30%) patients had solid tumors, 48 (12.2%) patients had hematological malignancies, 77 (19.6%) patients had diabetes mellitus, 124 (31.6%) patients had chronic cardiac disease, 52 (13.2%) patients had chronic pulmonary disease, 42 (10.7%) patients had chronic renal failure, 26 (6.6%) patients' skin barrier had been considered compromised, 244 (62.1%) patients had prior surgical intervention, 54 (13.7%) patients with corticosteroid use, 88 (22.4%) patients had prior antifungal agents use, 255 (64.9%) patients received antibiotics prior *Candida* BSI onset. 244 (72%) patients had at least two co-morbidities. No patient had human immunodeficiency virus (HIV) infection. Regarding the severity, 309 (78.6%) patients had fever, 180 (45.8%) patients received parenteral nutrition, 147 (37.4%) patients received mechanical ventilation, 49 (12.5%) patients received renal replacement therapy, and 42 (10.7%) patients had neutropenia. The clinical characteristics of patients, by *Candida* species, are shown in Table 2.

Table 2
Underlying disease and clinical feature of *Candida* blood stream infection [n (%)]

	C. albicans	*C. parapsilosis*	*C. tropicalis*	*C. glabrata*	*C. guilliermondii*	*C. sake*	*C. krusei*	Other *Candida spp.*	Total
	(n = 141)	(n = 87)	(n = 69)	(n = 48)	(n = 20)	(n = 8)	(n = 5)	(n = 15)	(n = 393)
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. lipolytica* (2cases), *C. theae* (2 cases), *C.famata* (1case) and *C. haemulonii* (1 case).

Table 2 here

Candida **species and antifungal susceptibility testing**

393 *Candida* species were isolated in total. 141 (35.9%) of *Candida* BSI were due to *C. albicans*, followed by *C. parapsilosis*(87cases, 22.1%), *C. tropicalis*(69cases, 17.6%), *C. glabrata*(48cases, 12.2%), *C. guilliermondii*(20cases, 5.1%), *C. sake*(8cases, 2.0%), *C.krusei*(5cases, 1.3%), and 15 other species (4 *C. gum*, 3 *C. lusitaniae*, 2 *C. intermedia*, 2 *C. theae*, 2 *C. lipolytica*, 1 *C. famata*and 1 *C. haemulonii*).

Among 393 *Candida* species, there were 378 episodes with antifungal susceptibility testing results. According to CLSI breakpoints 2012 (CBPs). As shown in Table 3, the susceptibility of *C. albicans, C. parapsilosis* to fluconazole and voriconazole were quite high, compared to itraconazole (94%, 93.3% VS 82.1%). The susceptibility of *C. tropicalis* to triazoles fluconazole, voriconazole, or itraconazole was not satisfactory. Amphotericin B and 5-flucytosine remained superior to 95% susceptibility against common *Candida spp.*, except for *C. krusei* and *C. guilliermondii*. Because echinocandin susceptibility testing has not been carried out in our hospital, the relevant clinical data could not be obtained.

Table 3
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)	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)	0 (0)	54(14.3)
R	7 (5.2)	3 (3.5)	29 (43.3)	3 (6.4)	5 (100)	0 (0)	6 (31.6)	3 (25.0)	56(14.8)
Itraconazole									
S	110 (82.1)	75 (87.2)	25 (37.3)	0 (0)	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)	0 (0)	7 (36.8)	0 (0)	66(17.5)
R	18 (13.4)	4 (4.7)	38 (56.7)	7 (14.9)	3 (60.0)	0 (0)	6 (31.6)	3 (25.0)	79(20.9)
Voriconazole									
S	125 (93.3)	79 (91.9)	41 (61.2)	45 (95.8)	4 (80.0)	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)	0 (0)	3 (15.8)	0 (0)	9(2.4)
R	9 (6.7)	5 (5.8)	24 (35.8)	1 (2.1)	0 (0)	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)	8 (100)	18 (94.7)	11 (91.7)	372(98.4)
R	1 (0.7)	3 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.3)	1 (8.3)	6(1.6)
Flucytosin									
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)	20(5.3)
15 *Candida spp.* isolats did not have susceptibility test, *C. albicans* (7), C. *parapsilosis* (2), *C. tropicalis* (2) and *glabrata*, *theae*, *gum*, *haemulonii* each.									
Abbreviation: S, susceptible; R, resistance; SDD, susceptible dose dependence.									

Table 3 here

Antifungal therapy and outcome

Antifungal therapy was administered in 299 (76.1%) of the cases. 94 (23.9%) patients did not receive any antifungal treatment. Among the patients who received antifungal therapy, 247 (62.8%) received early appropriate antifungal therapy, and 52 (13.2%) received target antifungal therapy. Fluconazole was most frequently used as empirical therapy, followed by echinocandins and voriconazole. 18 (4.6%) patients with *Candida* BSI received combination therapy.

The overall, 28-day mortality rate was 28.5%. The mortality rate was significantly higher in internal medicine wards and ICUs than in surgical wards (37.2% and 34.7% vs. 16.9%, respectively, $P < 0.001$) (Fig. 3a). The mortality for those who received early appropriate or target antifungal therapy was 26.8% or 25.1% ($P = 0.012$ or $P = 0.046$), as compared to 39.3% for those who hadn't receive any antifungal therapy. However, there was no significant difference between the mortalities for those who received early appropriate antifungal therapy and for those who received target antifungal therapy (Fig. 3b).

In 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 associated with 28-day mortality. In 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), neutropenia (HR = 4.347; 95%CI 2.462–7.675; P < 0.001), were independent risk factors for 28-day mortality, while antifungal therapy (HR = 0.570; 95%CI 0.382–0.849; P = 0.006) was independent protective factor for 28-day mortality (Table 4).

Table 4
Multivariable Cox regression analysis for the risk factors about 28-day mortality of Candida bloodstream infection (393 episodes)

28-day outcome				Multivariable analysis	
	Survival (n = 281)	Death (n = 112)	P value	HR (95%CI)	P value
Gender, male [n (%)]	216(76.9)	76(67.9)	0.065	-	-
Age (years, Mean ± SD)	55.2 ± 19.5	63.6 ± 16.2	< 0.01	1.025(1.013–1.037)	< 0.001
Underlying disease				-	-
Solid tumor [n (%)]	91(32.4)	27(24.1)	0.106	-	-
Hematologic malignancy [n (%)]	32(11.4)	16(14.3)	0.428	-	-
Diabetes mellitus [n (%)]	49(17.4)	28(25)	0.088	-	-
Chronic Cardiac disease [n (%)]	72(25.6)	52(46.4)	< 0.01	-	0.105
Chronic Pulmonary disease [n (%)]	34(12.1)	18(16.1)	0.294	-	-
Chronic renal failure [n (%)]	20(7.1)	22(19.6)	< 0.01	2.018(1.234–3.299)	0.005
Skin barrier compromised [n (%)]	24(8.5)	2(1.8)	0.015	-	0.308
Prior surgical intervention (< 1month) [n (%)]	182(64.8)	62(55.4)	0.083	-	-
Corticosteroid use [n (%)]	40(14.2)	14(12.5)	0.652	-	-
Prior antifungal agents use (< 6month) [n (%)]	64(22.8)	24(21.4)	0.772	-	-
Severity of clinical feature				-	-
Fever (T > 38.2°C) [n (%)]	220(78.3)	89(79.5)	0.798	-	-
Parenteral nutrition [n (%)]	124(44.1)	56(50)	0.292	-	-
Mechanical ventilation [n (%)]	89(31.7)	58(51.8)	< 0.01	1.950(1.307–2.912)	0.001
Renal replacement therapy [n (%)]	32(11.4)	17(15.2)	0.305	-	-
Central venous catheter [n (%)]	227(80.8)	89(79.5)	0.766	-	-
Neutropenia [n (%)]	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)			

Table 4 here

Discussion

Our study showed that in our Tertiary-care hospital in Shanghai, the incidence of *Candida* BSI has increased steadily in the past 11 years. Several studies have shown a substantial increase in the past 2 decades, which was similar to our study[1, 8, 17]. Intensive use of broad-spectrum antibiotics may be the main cause. Also, gradually worsening hospitalized patient profiles, underlying co-morbidities including malignancy, and high frequency of surgeries may be predisposing risk factors for increased incidence.

C. albicans was still the foremost pathogen of *Candida* BSI. However, over the past two decades, increased rates of common non-C. *albicans Candida spp.* has been reported worldwide, which was also observed in our study (35.9% for C. *albicans.* and 64.1% for non-C. *albicans*). C. *parapsilosis* (34.5%), C. *tropicalis* (27.4%) and C. *glabrata* (19.0%) account for most of non-C. *albicans*[18, 19]. In this study, the incidence of C. *guilliermondii* was incredibly higher than in other studies (4.8% *vs.* 0.4%)[20]. This could be related to the higher rate of parenteral nutrition and surgery (45.8% and 62.1%) in the current study, as some research implies that intravenous nutrition and surgery were significant risk factors for *Candida* BSI due to *C. guilliermondii*.[21].

The antifungal susceptibility testing showed that the susceptibility of C. *albicans*,

C. *parapsilosis* and C. *sake* for fluconazole were quite high (94%, 89.5%, 100%), while the resistance rate of C. *tropicalis* for fluconazole was as high as 43.3%, which was significantly higher than in other studies abroad[22, 23]. This may deserve more attention from clinicians in actual application.

There were 23.9% of patients with *Candida* BSI didn't receive any antifungal therapy in the present study. It was partly because some patients died before or soon after diagnostic confirmation. Although echinocandins have been recommended as a first-line antifungal agent, due to its high price, fluconazole was still the most frequently used empirical antifungal therapy. The 28-day crude mortality rate was 28.5%; a statistically significant finding is that the 28-day mortality rate for *Candida* BSI in patients from surgical wards was quite low compared with other wards. The contributing factor needs further study.

Another finding in our study was that there was no significant difference in 28-day mortality rate between the patients who received early appropriate antifungal therapy and the patients who received target antifungal therapy (26.8% and 25.1%). So we further analyzed demographic data, underlying diseases, and clinical features between these two groups, the result showed that there were no significant differences between the two groups in age($p = 0.33$), sex($p = 0.89$), the number of underlying diseases($p = 0.32$) and the number of severe clinical features($p = 0.96$). The choice of antifungal agents between these two groups was further analyzed. In the early appropriate antifungal therapy group, the rate of azoles use was 50.6%, and the rate of echinocandin use was 30.3%; while in the target antifungal therapy group, the rate of azoles use was 65.4%, and the rate of echinocandin use was 17.3%. The rate of echinocandin use was lower in the target antifungal therapy group than in the early appropriate antifungal therapy group ($p = 0.038$). Is the lower rate of echinocandin use in the target antifungal therapy group one of the reasons that caused no significant difference in mortality between the two groups? Many studies have confirmed the important role of echinocandin in antifungal therapy. Echinocandin has been recommended as a first-line antifungal agent since 2009[13], with fluconazole as an acceptable alternative for selected patients, reflecting the efficacy demonstrated by echinocandins and increasing resistance observed with fluconazole[24, 25]. Therefore, we believe that the lower rate of echinocandin use in the delayed antifungal treatment group is unlikely to lead to a decrease in the 28-day mortality rate. Based on the above analysis, we think that early antifungal therapy has no significant impact on the 28-day mortality rate compared with target antifungal therapy. Many clinicians currently administrate empirical antifungal agents; our study result may have an impact on their traditional view. Overuse use of antifungal drugs inevitably leads to a waste of medical resources and the rise of resistance[26]. If taking empirical antifungal agents cannot improve mortality, we should take a second thought about it. There are several studies support our findings[10–12], they showed that the severity of illness (APACHE-II Score) affected short-term survival in patients with *Candida* infection, whereas the choice of initial antifungal agents did not affect short-term survival. Trifi's research implied that no beneficial impact of an empirical antifungal therapy on 28- day survival neither in preventing the occurrence of candidemia in non-neutropenic septic critically patients[27]. However, some studies had different opinions on the timing of antifungal agents' use. Bassetti's research showed that the use of antifungal agents within 48 hours of obtaining a positive *Candida* blood culture result is an independent protective factor for mortality during hospitalization[9]; Similarly, Tedeschi's research showed that the administration of appropriate antifungal agents within 72 hours after blood culture was a protective factor for mortality during hospitalization[28]. However, due to the single-centered and the retrospective natures of their studies, those results need to be confirmed by more studies. Despite that, our results have shown similar risk factors (for example, age, neutropenia, mechanical ventilation, etc.) and protective factors (antifungal therapy) for 28-day mortality to theirs.

Although our data have been collected from a large hospital in Shanghai, several limitations of this study should be taken into consideration. First and foremost, this was a retrospective study performed at a single center, which could lead to selection bias. Moreover, the severity of illness score (such as APACHE II score), the timing of CVC removal was not included because of missing data.

Conclusion

Our retrospective study showed that the incidence of *Candida* BSI has increased in the past 11 years in Shanghai. Although the percentage of non- C. *albicans* has been increasing, the C. *albicans* remained the most frequently isolated species. The mortality of patients with *Candida* bloodstream infection was quite high, especially for those in internal medicine wards. Antifungal therapy did improve the short-term survival of patients with *Candida* BSI. Whether we should initiate preemptive antifungal therapy or apply antifungal therapy after antifungal susceptibility test needs further discussion.

Abbreviations

BSI
bloodstream infections
SD

standard deviation
HR
hazard ratio
CI
confidence interval
ICU
intensive care units
HIV
human immunodeficiency virus

Declarations

Ethics approval and consent to participate:

The study was approved by the local institutional review board (Ruijin Hospital, Shanghai Jiaotong University, School of medicine) and written patient consent was not required because of the observational nature of this study.

Consent for publication:

Not applicable.

Availability of data and materials:

All data generated or analyzed during this study are included in this published article.

Competing interest:

The authors declare that they have no competing interests.

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Authors' contributions:

ZTY, EZC, and EQM made substantial contributions to conception and design. ZTY, 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.

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Figures

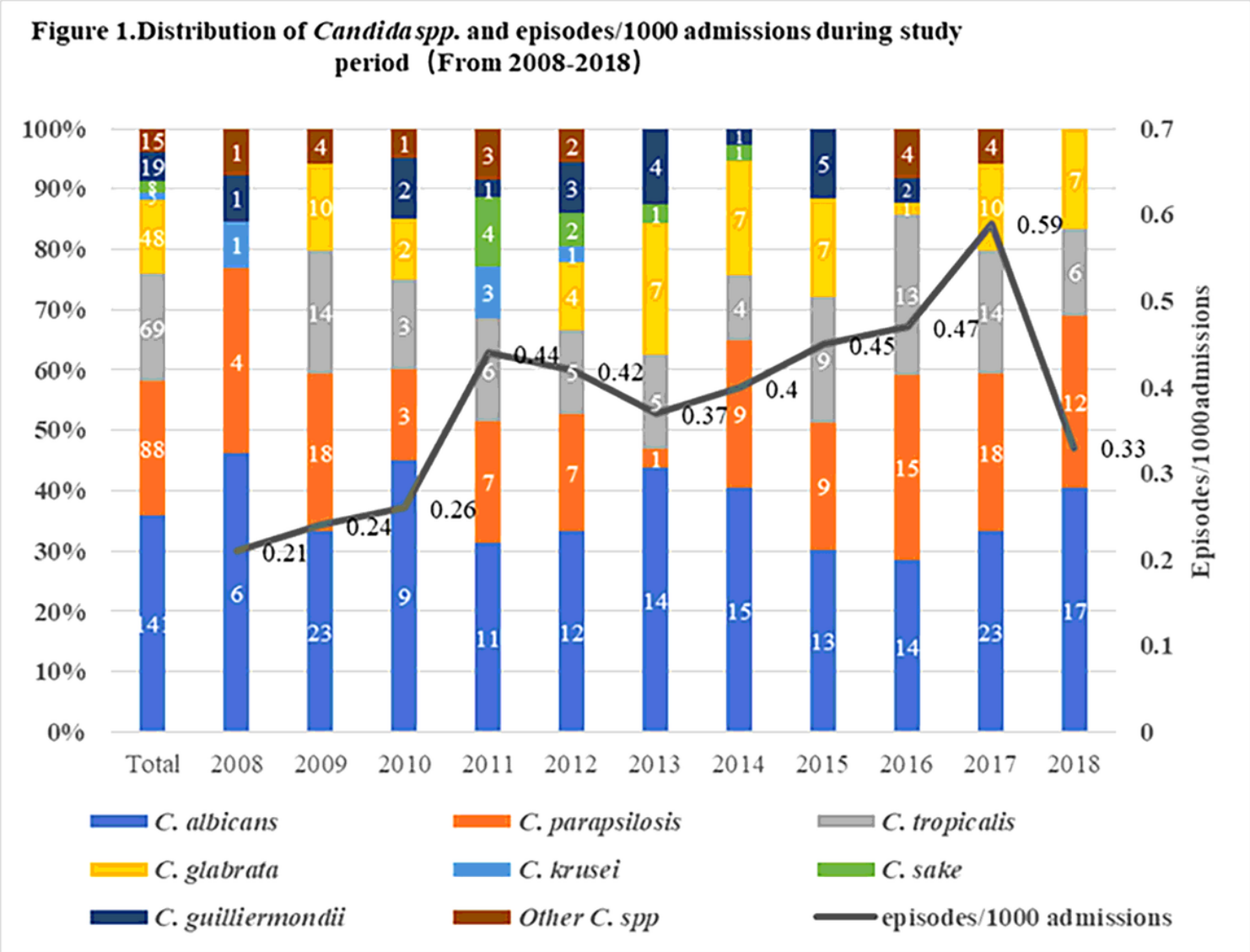


Figure 1

Distribution of Candida spp. and episodes/1000 admissions during study period (From 2008-2018).

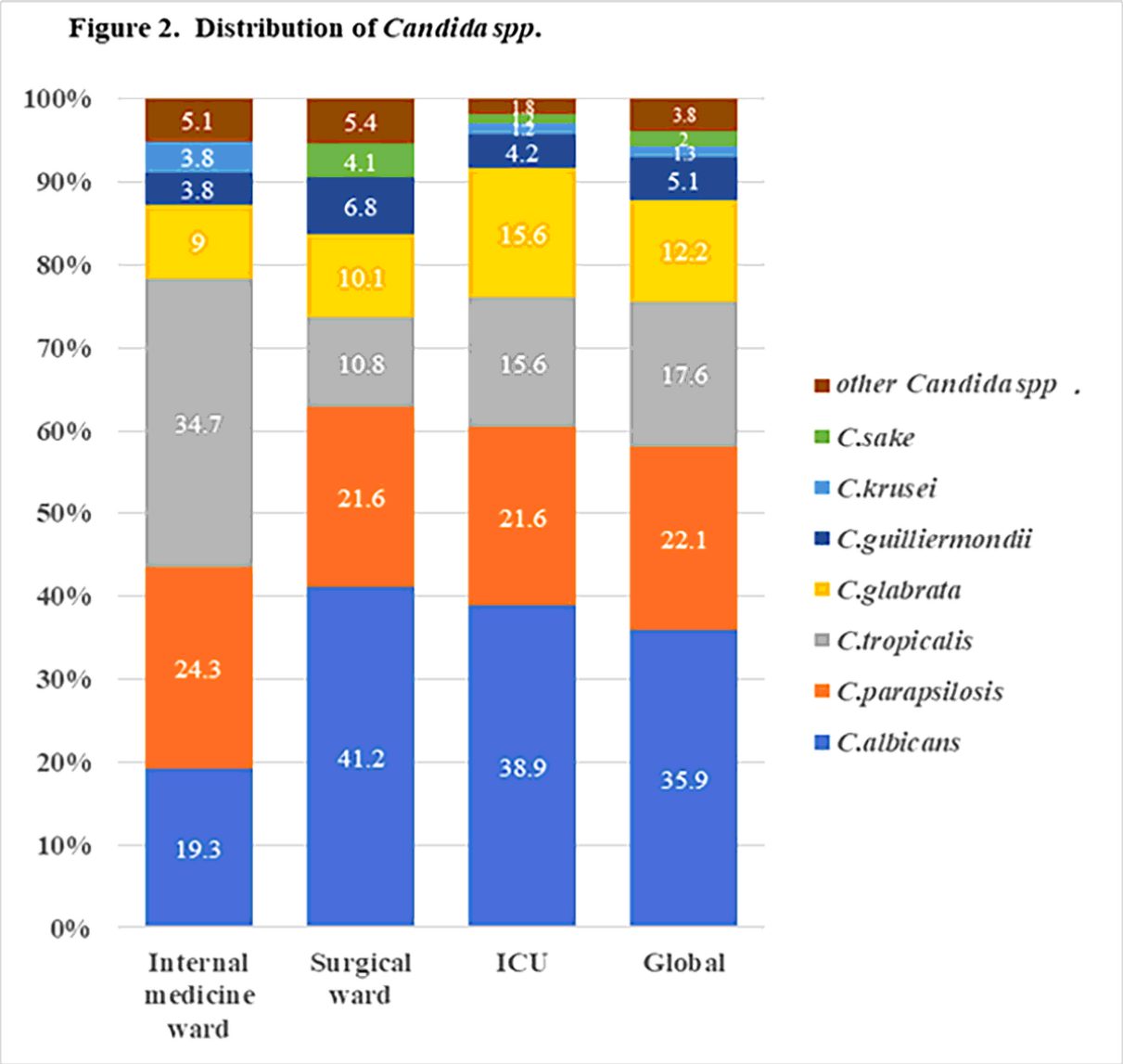
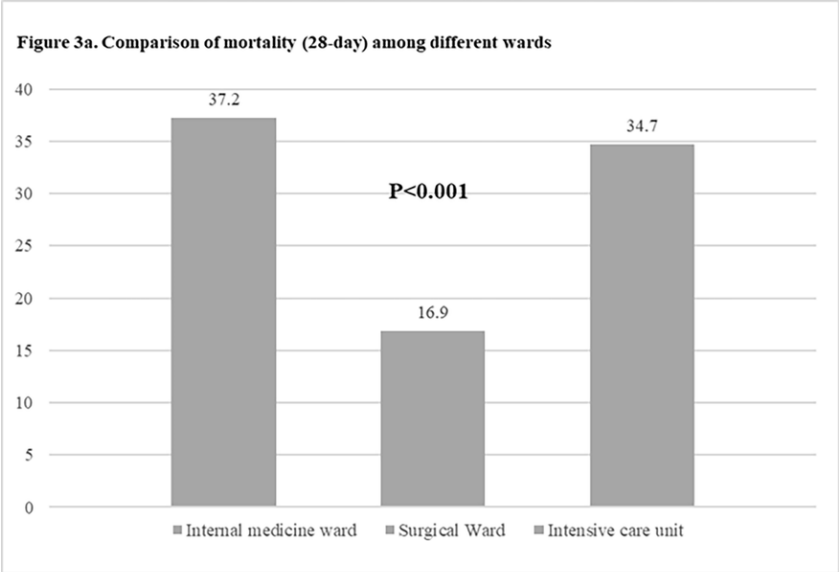


Figure 2

Distribution of Candida spp. 148 episodes were from the surgical ward, 167 episodes were from ICU and 78 episodes were from the internal medicine ward.



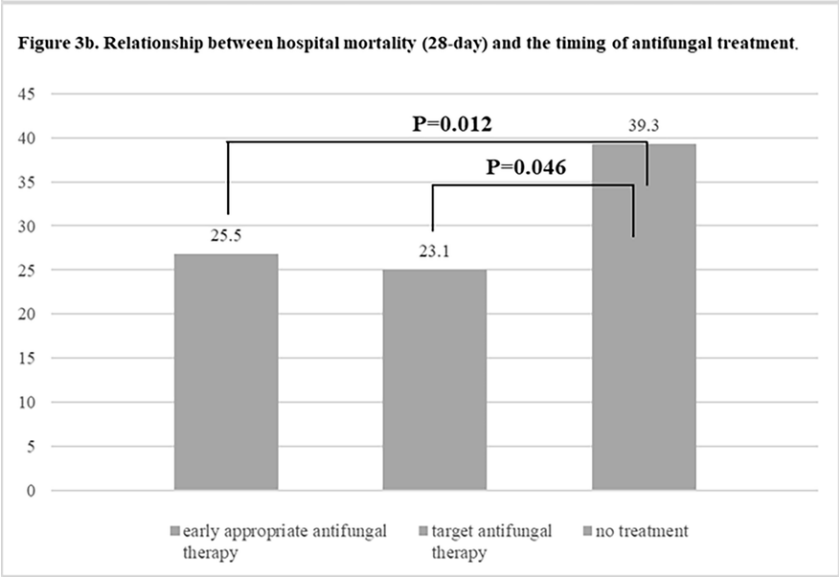


Figure 3

Figure 3a Comparison of mortality among different wards. The mortality rate was significantly higher in internal medicine wards and ICUs than in surgical wards Figure 3b Relationship between hospital mortality (28-day) and the timing of antifungal treatment. No significant difference between the mortalities for those who received early appropriate antifungal therapy and for those who received target antifungal therapy.