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An 11-Year retrospective analysis of candidiasis epidemiology, risk factors, and antifungal susceptibility in a tertiary care hospital in China

Sabir Khan[1,10], Lin Cai[1,10], Hazrat Bilal[2], Muhammad Nadeem Khan[3], Wenjie Fang[4], Dongxing Zhang[5,6], Fen Yao[7], Xun Wang[1], Qian Wang[1], Bing Hou[8], Jiayue Wang[9], Chunyan Mao[9], Lingxi Liu[9] & Yuebin Zeng[1,9]✉

Candidiasis poses a significant threat to human health, especially in immunocompromised patients. However, there is a paucity of epidemiological data concerning the prevalence of candidiasis in developing regions of China. We conducted a retrospective study on patients positive for *Candida* infections in a tertiary care hospital in Shantou, China, to identify the clinical characteristics and risk factors for candidiasis. Of 5,095 cases of candidiasis, 489 (9.59%) were candidemia infections. *Candida albicans* (*n* = 230, 47.0%) was the predominant species identified among all patients. Non-*albicans Candida* (NAC) was more prevalent in adult patients, while *Candida glabrata* was slightly more frequent in pediatric patients (*n* = 10, 14.7%). Pulmonary diseases (*n* = 200, 47.8%) were the most common underlying comorbidities in adult patients (*n* = 25, 35.2%). Thrombocytopenia was the only laboratory finding higher in adult patients than in pediatric patients. Respiratory dysfunction, the presence of a central venous catheter, septic shock, and thrombocytopenia were independent risk factors for candidemia-related 30-day mortality. Amphotericin B exhibited high efficacy (100%), and itraconazole exhibited the lowest efficacy against all tested *Candida* isolates. *C. glabrata* had a lower susceptibility to azole, although this was not statistically significant. The epidemiological data on candidiasis, specifically candidemia in pediatric and adult patients, varied regarding the prevalence of *Candida* species and associated risk factors. This study provides guidance for prescribing the appropriate therapy and yields insights into the susceptibility patterns of different *Candida* isolates to antifungal drugs.

Keywords Candidiasis, Candidemia, Epidemiology, Risk factors, Antifungal susceptibility

Abbreviations

NAC	Non-albicans Candida
IC	Invasive candidiasis
CVC	Central Venous Catheterization
MALDI-TOF-MS	Matrix-assisted laser desorption ionization-time of flight mass spectrometry

[1]Department of Dermatology, Second Affiliated Hospital of Shantou University Medical College, Shantou 515041, China. [2]Jiangxi Key Laboratory of oncology, The Second Affiliated Hospital of Nanchang Medical College, Jiangxi Cancer Hospital, Jiangxi Cancer Institute, Nanchang 330029, Jiangxi, P.R. China. [3]Deparment of Cell Biology and Genetics, Shantou University Medical College, Shantou, China. [4]Department of Dermatology, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China. [5]Department of Dermatology, Meizhou Dongshan Hospital, Meizhou 514023, Guangdong Province, China. [6]Department of Dermatology, Meizhou People's Hospital, Meizhou 514023, Guangdong Province, China. [7]Department of Pharmacy, Shantou University School Medical College, Shantou, China. [8]Deparment of Clinical Laboratory, Skin and Venereal Diseases Prevention and Control Hospital of Shantou City, Shantou, Guangdong, China. [9]Department of Dermatology, West China Second University Hospital, Sichuan University, Chengdu 610021, Sichuan, China. [10]These authors contributed equally: Sabir Khan and Lin Cai. ✉email: zeng_yb@163.com

AMB	amphotericin B
FC	flucytosine
FCA	fluconazole
ITR	itraconazole
VRC	voriconazole
ICU	intensive care unit
PICU	pediatric intensive care unit
NICU	neonatal intensive care unit

Candida is an opportunistic fungal pathogen that causes superficial or invasive infections in immunocompromised individuals[1,2]. Invasive candidiasis (IC), which presents in severe forms such as bloodstream *Candida* infections (candidemia) and deep-seated infections, most often occurs in hospitalized patients[1,2]. Candidemia is associated with high morbidity and mortality rates[3]. However, the global incidence of candidemia varies according to the local epidemiology, geographic location, patient gender, age, and other factors. Based on single and multicenter investigations, estimates of candidemia rates range from 0.21 to 5 per 1,000 admitted patients[4–7]. The onset of candidemia leads to difficulties in treatment and often extends hospital stays, thereby imposing a significant burden on patients and healthcare systems[8,9].

More than 40 species of *Candida* are known to cause candidemia. *C. albicans* is the most prevalent species identified in epidemiological studies[10]. However, the prevalence of non-*albicans Candida* (NAC) candidemia has been increasing across different age groups[11–16]. *C. tropicalis*, C. *glabrata*, *C. parapsilosis*, and *C. krusei* are the predominant species associated with NAC. Each *Candida* species has a unique invasive ability, virulence, tissue tropism, and antifungal sensitivity profile[17,18]. The risk factors for candidemia include cardiovascular disease, gastrointestinal pathology, diabetes mellitus, hematologic malignancies, respiratory dysfunction, respiratory diseases, solid-organ tumors, low birth weight in neonates and preterm infants, broad-spectrum antimicrobial agent use, total parenteral nutrition, central venous catheterization (CVC), hemodialysis, surgery, and thrombocytopenia[4,19–21]. Studies in different regions of China have shown that the prevalence of *Candida* species (both *C. albicans* and NAC) and infection risk factors vary geographically and among age groups. Therefore, local epidemiological and surveillance studies are required for the prevention and treatment of candidemia.

The susceptibility of *Candida* pathogens to antifungal agents is a matter of concern owing to the limited availability of antifungal drugs and the emergence of multi-drug resistant strains[18,22]. Early and appropriate treatment is crucial for improving overall outcomes in individuals with candidemia[23–25], requiring prompt administration of specific antifungal therapy. Comprehensive local epidemiological data and knowledge of antifungal susceptibility profiles and trends are crucial for selecting the initial antifungal treatment[26–28]. A recent systematic study in China reported the susceptibility profiles of various *Candida* species to antifungal agents and compared the results to other regions worldwide[29]. The study also reported that susceptibility profiles varied among regions of China. Therefore, studying the susceptibility profiles of antifungal agents is necessary for proper antifungal treatments. It is also important to collect epidemiological data on both pediatric and adult patients in local regions.

Azoles are the most commonly used antifungal therapy against candidiasis, followed by echinocandins, while polyenes are rarely prescribed due to their toxicity. Switching antifungal therapy may be necessary in cases of drug resistance, treatment failure, or patient intolerance[30]. The therapeutic efficacy of antifungal drugs against candidiasis depends on the strain type, severity of the infection, and underlying morbidities. The emergence of antifungal resistance, poor drug absorption in some patients, and drug-drug interactions also affect the efficacy of antifungal agents. Therefore, the microbiological, clinical, and pathological conditions of patients need to be closely monitored for the appropriate adjustment of treatment dosage[31].

The current study investigated the incidence, risk factors, and antifungal drug susceptibility associated with candidiasis over 11 years at the Second Affiliated Hospital in Shantou, Guangdong, China. The study provides crucial clinical data on the distribution, risk factors, and antifungal susceptibility profiles of various Candida pathogens associated with candidiasis, specifically those causing candidemia in pediatric and adult patients. Our findings will provide relevant information for healthcare officials and prescribers, thereby aiding in the formulation of strategies to control candidemia in the region.

Methods

Patient data collection

The current retrospective analysis spanned 11 years from 2011 to 2021 and was conducted at a 1500-bed tertiary facility (Hospital A) under the administration of the Shantou Second Affiliated Hospital. This facility provides health services to 4.5 million people in Shantou City, China. *Candida* infections were diagnosed according to the guidelines for candidiasis management established by the China Medical Association and the Infectious Diseases Society of America[32,33]. The demographic data and clinical characteristics of patients with candidiasis were collected from the hospital's electronic medical records. The study examined the mortality rate from one week to one month based on patient age, gender, admission ward, underlying comorbidities, and previous invasive procedures performed over the previous month.

Microbiological methods and susceptibility testing

Candida species were isolated from biological specimens obtained from patients using appropriate protocols, followed by direct microscopy with potassium hydroxide. Blood was inoculated in BacT/AlerT 3D (bioMérieux, France) and cultured aerobically and anaerobically on CHROMagar-*Candida* medium. All *Candida* isolates were identified by Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS) using the MALDI Biotyper RTC 4.0 package (Bruker Diagnostics, Inc., USA). Antifungal susceptibility

testing of five drugs, amphotericin B (AMB), flucytosine (FC), fluconazole (FCA), itraconazole (ITR), and voriconazole (VRC), was conducted for the isolated strains using the ATB FUNGUS 3 kit (bioMérieux, France) that is commonly used in China[34]. The strain *C. krusei* ATCC (6258) and *C. parapsilosis* ATCC (22019) were used for quality control[18]. The interpretation of susceptibility testing results followed the guidelines established by the Clinical & Laboratory Standards Institutes (CLSI)[35,36].

Interpretation of MIC results

MIC data were analyzed using the CLSI protocol M27-S4, and interpretation of susceptibility was performed by using CLSI clinical breakpoints (CBPs)[35,37], or epidemiological cutoff values (ECVs) were applied, where CBPs were not available[38,39] (Table S1). In case CBPs absent data, isolates were distributed as a wild-type (WT) or a non-WT (NWT) drug susceptibility phenotype according to the ECVs as determined by the CLSI broth microdilution method[35,37].

Definitions

Candidemia was defined as the detection of a species of *Candida* in the first blood culture of a patient, along with associated clinical signs and symptoms. Regarding age categorization, individuals aged from one day to 17 years were considered pediatric patients, and those 18 to 98 years of age were considered adult patients. *Candida* infections associated with candidemia were examined, along with the demographic and clinical characteristics of pediatric and adult patients. Laboratory test results were collected at the onset of candidemia. Renal failure was defined as a serum creatinine level above 62 µmol/l for pediatric patients and 104 µmol/l for adult patients. Anemia was defined as a hemoglobin level below 105 g/l. Thrombocytopenia was defined as a platelet count level $< 150 \times 10^9$/l for pediatric and $< 100 \times 10^9$/l for adult patients. Hyponatremia was defined as having a serum sodium level < 135 mmol/l and hypernatremia as a serum sodium level > 145 mmol/l. Treatment with antifungal agents was considered empirical when it was initiated before obtaining susceptibility test results. Results were recorded 30 days following the onset of candidemia.

Statistical analysis

The clinical data from the electronic medical records of Shantou Second Affiliated Hospital were extracted into an Excel file (2021) by two independent researchers (SK and LC). The files were cross-checked and compared to remove any possible biases. The outcome variables were presented as relative percentages and absolute values, and quantitative variables were calculated as medians and interquartile ranges. A chi-square test was performed for the univariate analysis of baseline characteristics to test the associations between infections and patients. All statistical analyses and graphical visualization were performed using GraphPad Prism *v*.8.0.2.

Ethics approval

Ethical approval was provided by the Second Affiliated Hospital of Shantou University Medical College, Human Research Ethics Committee (Ref. 2022 – 167) following the Declaration of Helsinki criteria. The ethics committee waived patient consent, as all the clinical samples were obtained from the Second Affiliated Hospital of Shantou University Medical College laboratory for routine work and not for this study.

Results

The distribution of Candida species

A total of 5,095 cases of *Candida* infection were documented over the 11-year study period, with a significant preponderance of *C. albicans* isolates ($n = 2{,}863$, 56.19%), followed by *C. tropicalis* ($n = 1007$, 19.76%), *C. glabrata* ($n = 611$, 11.99%), *C. parapsilosis* ($n = 343$, 6.73%), and *C. krusei* ($n = 167$, 3.27%). The prevalence of *Candida* species is shown in Table 1. The patients' median age was 63.5 years (range, one day–98 years). Among the age groups, *Candida* infections more commonly occurred in adult patients ($n = 3{,}915$, 76.8%) than in pediatric patients ($n = 1{,}180$, 33.1%). Higher proportions of *Candida* infections were reported in males ($n = 3{,}026$, 59.3%) than in females ($n = 2{,}070$, 40.6%). The incidence of *Candida* species increased over time (Table 1). The incidence of *C. albicans* increased from 2.1 per 1,000 patients in 2011 to 3.2 in 2021. The medical wards reported the majority of *Candida* infections ($n = 1{,}306$, 25.62%), followed by intensive care units (ICUs; $n = 2651$, 52.02%), pediatric wards ($n = 913$, 17.91%), and surgical wards ($n = 225$, 4.41%).

Candidemia

A total of 489 candidemia cases were reported during the study period. *C. albicans* was predominant ($n = 230$, 47.0%), followed by *C. tropicalis* ($n = 95$, 19.4%), *C. glabrata* ($n = 69$, 14.1%), *C. parapsilosis* ($n = 46$, 9.40%), and *C. krusei* ($n = 27$, 5.52%). The distribution of *Candida* species is shown in Table 2. Among pediatric patients, a high proportion of infections were caused by *C. albicans* ($n = 37$, 54.4%). The proportion of *C. glabrata* ($n = 10$, 14.7%) was slightly higher in pediatric than in adult patients, while other NAC species were found more frequently in adult patients. The proportions of other *Candida* species in different age groups are shown in Fig. 1a. The majority of patients were male ($n = 280$, 57.2%). *Candida* species were more frequent in male patients than in female patients, except for *C. parapsilosis* and *C. krusei*, with respective ratios of 0.53:1 and 0.68:1. Among hospital departments, the medical wards ($n = 207$, 42.3%) recorded the highest number of cases, followed by ICUs ($n = 151$, 30.8%), surgical wards ($n = 97$, 19.8%), and pediatric wards ($n = 34$, 6.95%). *C. albicans* ($n = 91$, 60.2%) was identified in high proportions in the ICU/pediatric (PICU)/neonatal (NICU) department. Among NAC species, *C. tropicalis* ($n = 58$, 28.0%), and *C. glabrata* ($n = 29$, 29.8%) were dominant in medical wards and surgical wards, respectively (Fig. 1b).

One or more comorbidities were identified in most patients. Comorbidities in adult patients were significantly more frequent than in pediatric patients ($P < 0.05$). Thrombocytopenia was more frequent in older patients than

	Candida species, *n*=, (%)						
Distribution	**Total *n*=5,095 (100%)**	**C. albicans *n*=2,863 (56.19%)**	**C. tropicalis *n*=1,007 (19.76%)**	**C. glabrata *n*=611 (11.99%)**	**C. parapsilosis *n*=343 (6.73%)**	**C. krusei *n*=167 (3.27%)**	**Other *n*=105 (2.06%)**
Age Group							
Pediatric patients (≤17 years)	1,180 (23.1)	649 (55.0)	245 (20.7)	124 (10.5)	57 (4.83)	53 (4.49)	52 (4.40)
(0–28 days)	98 (1.92)	47 (47.9)	32 (32.6)	8 (8.16)	4 (4.08)	7 (7.14)	0
(1 month-1 year)	136 (2.66)	69 (50.7)	28 (20.5)	19 (13.9)	8 (5.88)	6 (4.41)	9 (6.61)
(<1 year- 17 years)	946 (18.5)	533 (56.34)	185 (19.5)	97 (10.2)	45 (4.75)	40 (4.22)	43 (4.54)
Adult patients	3,915 (76.8)	2,214 (56.5)	762 (19.4)	495 (12.6)	284 (7.25)	108 (2.75)	53 (1.35)
17–65 years	2113 (41.4)	1180 (58.8)	416 (19.68%)	258 (12.21%)	161 (7.61%)	65 (3.07%)	34 (1.60%)
65–98 years	1802 (35.3)	1034 (57.38%)	346 (19.20%)	237 (13.15%)	123 (6.82%)	43 (2.38%)	19 (1.05%)
Gender Group							
Male	3026 (59.3)	1727 (57.54%)	660 (21.99%)	299 (9.96%)	184 (8.78%)	91 (3.03%)	65 (2.14%)
Female	2070 (40.6)	1136 (54.22%)	347 (16.56%)	312 (14.89%)	159 (5.29%)	76 (3.62%)	40 (1.93%)
Ratio	1.43:1.0	1.52:1.0	1.90:1.0	0.95:1.0	1.15:1.0	1.19:1.0	1.62:1.0
Incidence/1,000 Patients							
2011	0.28	2.1	0.55	0.47	0.33	0.14	0.11
2012	0.25	2.3	0.48	0.57	0.27	0.07	0
2013	0.25	2.4	0.64	0.5	0.35	0.15	0.13
2014	0.12	1.8	0.51	0.35	0.21	0.14	0
2015	0.25	2.1	0.59	0.37	0.23	0.22	0.11
2016	0.25	2.9	0.61	0.66	0.30	0.05	0.15
2017	0.25	2.3	0.71	0.49	0.21	0.13	0.07
2018	0.37	2.7	1.62	0.57	0.31	0.14	0.05
2019	0.50	3.2	1.55	0.70	0.36	0.24	0.12
2020	0.50	3.1	1.94	0.65	0.45	0.22	0.12
2021	0.37	3.2	0.87	0.72	0.42	0.17	0.19
Means	0.25	2.55	0.91	0.55	0.31	0.15	0.09

Table 1. Distribution and incidence of Candida species. Other: *C. lusitaniae* *n*=59 (1.15%), *C. metapsilosis* *n*=24 (0.47%), *C. norvegensis* *n*=22 (0.43%).

in pediatric patients ($P<0.05$). The all-cause mortality rates for candidemia were 27 (5.52%), 97 (19.8%), and 125 (25.5%) at 7 days, 30 days, and overall, respectively. The mortality at 30 days was 6 (5.63%) in pediatric patients and 91 (21.7%) in adult patients ($P<0.05$; Table 3).

The univariate predictors associated with outcomes of candidemia are listed in Table 4. For pediatric patients with candidemia, the factors of respiratory dysfunction, UTIs, and renal failure were linked with 30-day mortality. For adult patients with candidemia, cardiovascular disease, respiratory dysfunction, pulmonary diseases, central venous catheter, urinary tract catheter, septic shock, mechanical ventilation, and thrombocytopenia were linked with 30-day mortality. The results of an odds ratio analysis for independent risk factors are listed in Table 5. Respiratory dysfunction was an independent risk factor for 30-day mortality in adults and all patients. A central venous catheter, mechanical ventilation, septic shock, and thrombocytopenia were significant factors for 30-day mortality in adults and all patients. The odds ratio for pediatric patients was not analyzed due to the small number of deaths (6/71).

Antifungal susceptibility

The antifungal susceptibility profiles of all *Candida* species are summarized in Table 6. Among total isolates, itraconazole had relatively high MIC values ranging from 0.12 to 1 for MIC50 and 0.5 to 4 for MIC90. *C. parapsilosis* had the highest percentage of itraconzole NWT isolates (43/141, 30.4%), followed by *C. albicans* (524/1880, 27.8%), *C. glabrata* (55/391 ,14.0%), *C. krusei* (10/94, 10.6%) and *C. tropicalis* (4/256, 1.12%). Similarly, fluconazole showed high susceptibility against *C. parapsilosis* (21.8%), followed by *C. albicans* (11.9%), *C. glabrata* (6.31%), and *C. tropicalis* (3.67%).

The susceptibility profiles of *Candida* isolates obtained from bloodstream *Candida* infections (BSCI) were compared with those of non-bloodstream *Candida* infections (non-BSCI); see Fig. 2. For *C. albicans* and *C.*

Distribution *n* (%)	Total (*n* = 489)	C. albicans 230 (47.0)	C. tropicalis 95 (19.4)	C. glabrata 69 (14.1)	C. parapsilosis 46 (9.40)	C. krusei 27 (5.52)	Others 22 (4.49%)
Pediatric patients							
(≤ 17 years)	68 (13.9)	37 (54.4)	12 (17.6)	10 (14.7)	2 (2.94)	2 (2.94)	0
(0–28 days)	41 (8.38)	22 (53.6)	6 (14.6)	7 (17.0)	2 (4.89)	2 (4.87)	0
(1 month-1 year)	8 (1.63)	5 (62.5)	1 (12.5)	1 (12.5)	0	0	0
(< 1 year- 17 years)	19 (3.88)	10 (52.6)	5 (26.3)	2 (10.5)	0	0	0
Adult patients (> 16 years)	421 (61.9)	193 (45.8)	83 (19.7)	59 (14.0)	44 (10.4)	23 (5.46)	22 (5.22)
17–50 years	197 (40.2)	97 (49.2)	51 (25.8)	14 (7.10)	8 (4.06)	15 (7.61)	12 (6.09)
50–65 years	102 (20.8)	57 (50.9)	19 (18.6)	16 (15.6)	4 (1.99)	4 (3.92)	5 (4.90)
< 65–98 years	122 (24.9)	39 (31.9)	13 (10.6)	29 (23.7)	32 (26.2)	4 (3.27)	5 (4.09)
Male	280 (57.2)	141 (50.3)	54 (19.2)	43 (15.3)	16 (5.71)	11 (3.92)	15 (5.35)
Female	209 (42.7)	89 (42.5)	41 (19.6)	26 (12.4)	30 (14.3)	16 (7.65)	7 (3.34)
Ratio	1.33:1	1.58:1	1.31:1	1.65:1	0.53:1	0.68:1	2.1:1
Hospital departments							
Medical wards	207 (42.3)	83 (40.0)	58 (28.0)	18 (8.69)	20 (9.66)	13 (6.28)	15 (7.24)
ICU/PICU/NICU	151 (30.8)	91 (60.2)	20 (13.2)	16 (10.5)	12 (7.94)	6 (3.97)	6 (3.97)
Surgical wards	97 (19.8)	42 (43.2)	12 (12.3)	29 (29.8)	6 (6.18)	7 (7.21)	1(1.03)
Pediatric wards	34 (6.95)	14 (41.1)	5 (14.7)	6 (17.6)	8 (23.5)	1 (2.94)	0

Table 2. *Candida* species isolated from the blood sample by age group (*n* = 489). **Others**: *C. lusitaniae* 15 (3.06%), *C. metapsilosis* 5 (1.02%), *C. norvegensis* 2 (0.40%).

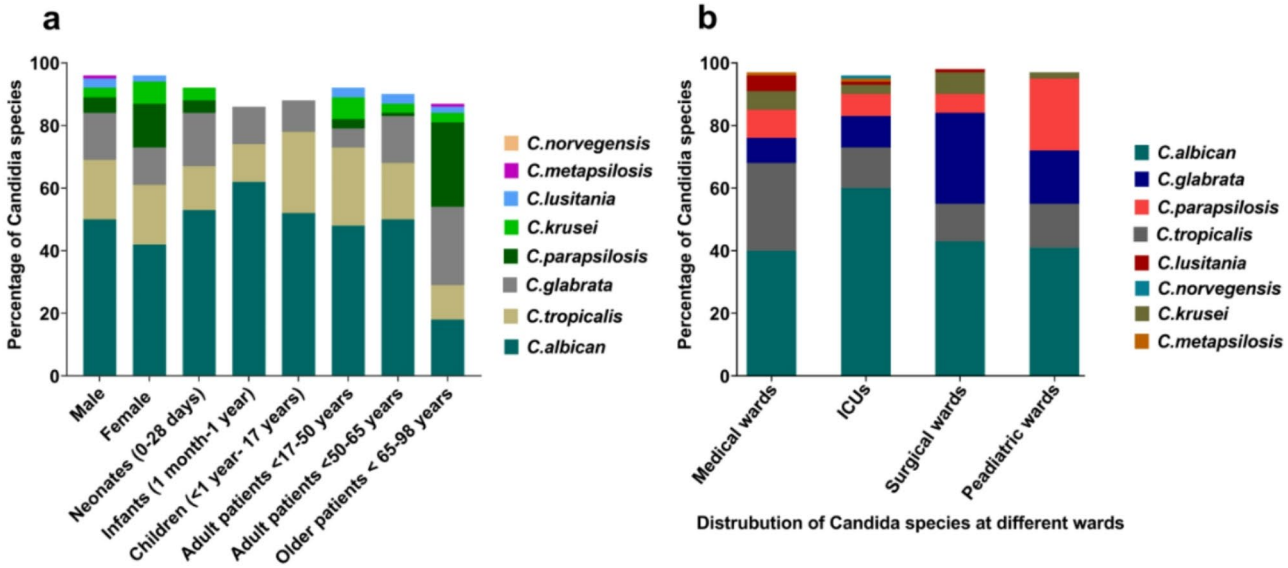

Fig. 1. The distribution of *Candida* species. (a) The prevalence of *Candida* species identified in different age groups. (b) Percentages of *Candida* species in different wards.

parapsilosis, VRC exhibited higher efficacy in the BSCI group compared to the non-BSCI group ($P < 0.05$). For *C. tropicalis*, FCA exhibited higher efficacy in the BSCI than in the non-BSCI group ($P > 0.05$). Similarly, *C. glabrata* demonstrated lower susceptibility to ITR and VRC in the BSCI compared to the non-BSCI group ($P < 0.05$). For *C. krusei*, FC demonstrated higher efficacy in the BSCI group than in the non-BSCI group. *C. krusei* showed lower susceptibility to VRC and ITR in the BSCI than in the non-BSCI group ($P > 0.05$).

Discussion

Invasive candidiasis and deep-seated infections largely occur in hospitalized patients. In addition, superficial, oral, and vaginal candidiasis cases have been reported[29]. In this 11-year retrospective study, we analyzed the distribution, clinical characteristics, underlying comorbidities, risk factors, and antifungal susceptibility profiles of pathogenic *Candida*. Moreover, we conducted epidemiological comparisons between pediatric and adult patients using data from a tertiary care hospital in Shantou, China. To our knowledge, this is the first epidemiological study comparing the occurrence of candidiasis between pediatric and adult patients in

Variables	Total; *n* (%) 489 (100%)	Pediatric patients (0–17 years); *n* (%) 71 (22.53%)	Adult patients (18–98 years); *n* (%) 418 (85.48%)	*p*-value
Age (Median, range)	63.5 years (1 day, 98 years)	1 day (1 day,8 years)	68 years (65 years, 98 years)	< 0.001
Male	277 (56.6)	43 (60.5)	234 (55.9)	0.47
Female	212 (43.3)	28 (39.4)	184 (44.0)	0.46
Underlying comorbidities (n, %)				
Cardiovascular disease	162 (33.1)	5 (7.04)	157 (37.5)	0.001
Diabetes mellitus	136 (27.8)	6 (8.45)	130 (31.1)	0.001
Gastrointestinal pathology	116 (23.7)	2 (2.81)	114 (27.2)	0.001
Hematologic malignancy	21 (4.29)	3 (4.22)	18 (4.30)	0.98
Liver disease (acute or chronic)	119 (24.3)	11 (15.4)	108 (25.8)	0.06
Oral cavity	60 (12.2)	26 (36.6)	34 (8.13)	0.001
Renal failure	48 (9.81)	6 (8.45)	42 (10.0)	0.68
Respiratory dysfunction	177 (36.1)	17 (23.9)	160 (38.2)	0.02
Septic shock	170 (34.7)	24 (33.8)	146 (34.9)	0.001
Solid tumor	18 (3.68)	0	18 (4.30)	0.07
Skin barrier	38 (7.77)	9 (12.6)	29 (6.93)	0.09
Surgery	32 (6.54)	6 (8.45)	26 (6.22)	0.48
Pulmonary diseases	225 (46.0)	25 (35.2)	200 (47.8)	0.05
Tuberculosis	30 (6.13)	5 (7.04)	25 (5.98)	0.73
Neurological diseases	21 (4.29)	5 (7.04)	16 (3.82)	0.22
UTI	28 (5.72)	2 (2.81)	26 (6.22)	0.25
Empirical Theraphy				
Previous therapy with antibiotics	228 (46.6)	47 (23.9)	181 (43.3)	0.003
Treatment with antifungal agents	159 (32.5)	14 (19.7)	142 (33.9)	0.02
Indwelling devices				
Central venous catheter	81 (16.5)	15 (21.2)	48 (11.4)	0.02
Urinary tract catheter	167 (34.1)	18 (25.3%)	149 (35.6)	0.09
Total parenteral nutrition	47 (9.61)	10 (14.0)	37 (8.85)	0.17
Mechanical ventilation	119 (24.3)	21 (29.5)	98 (44.9)	0.27
Other variable				
ICU/PICU/NICU	214 (43.7)	41 (57.7)	173 (79.3)	0.01
Malnutrition	60 (12.2)	12 (16.9)	48 (11.4)	0.20
Laboratory findings				
Anaemia	146 (29.8)	27 (38.0)	119 (23.6)	0.10
Thrombocytopaenia	62 (12.7)	15 (21.1)	47 (11.2)	0.02
Hyponatraemia	150 (30.7)	28 (39.4)	122 (29.1)	0.08
Hypernatremia	30 (6.13)	6 (8.45)	24 (5.74)	0.38
Mortality				
7 days mortality	27 (5.52)	4 (5.63)	23 (5.50)	0.96
30 days mortality	97 (19.8)	6 (5.63)	91 (21.7)	0.009
All-cause mortality	125 (25.5)	10 (14.0)	115 (27.5)	0.07

Table 3. Demographic data and clinical characteristics of candidemia patients.

Southern China. The findings provide in-depth information for healthcare workers, thereby contributing to a better understanding and control of candidiasis, especially candidemia.

There was a high prevalence of *C. albicans* causing candidiasis across all patient age groups. This finding aligns with a recent report that describes a high percentage of *C. albicans* among patients in South China hospitals[18]. However, some studies have also reported a high proportion of NCA[40]. In pediatric patients, *C. tropicalis* was dominant among NCA, followed by *C. glabrata* and *C. parapsilosis.* The epidemiology of *Candida* species depends on various factors, including region, patient type, and diagnostic center. Notably, a high proportion of *C. tropicalis* compared to *C. glabrata* has been reported in studies from India, Canada, China, and Italy[4,20,21,41,42]. *C. tropicalis* is also highly prevalent, causing candidemia in pediatric and adult patients. In pediatric patients (0–28 days), *C. glabrata* was identified in a relatively high proportion of patients, as previously reported in Southwest China. In patients < 65–98 years old, there was a high proportion of *C. parapsilosis*, followed by *C. glabrata* and *C. tropicalis*.

In cases of candidemia, a high prevalence of *C. albicans* has been reported in different regions of China and other Asian countries such as Iran, Kuwait, Japan and Saudia arabia. Among NCA in candidemia patients, a significant prevalence of *C. tropicalis* has similarly been reported in regions of China at similar latitudes as in

Variables	*Child patients (0–17 years)* **30 days outcome** *Survive Died* ***n*** **= 65** ***n*** **= 6**		***p*-value**	*Adult Patients (18–98 years)* **30 days outcome** *Survive Died* ***n*** **= 327** ***n*** **= 91**		***p*-value**	*All patients* **30-days outcome** *Survive Died* ***n*** **= 392** ***n*** **= 97**		***p*-value**
Age (Median, range)	1 day (1 day,8 years)	1 day (1 day, 1 day)	0.658	18 years (25 years, 98 years)	29 year (38 years, 94 years)	0.001	51 years (1 day, 98 years)	64 years (1 day, 88 years)	0.001
Male	39 (60.0)	4 (66.6)	0.75	182 (55.6)	52 (57.1)	0.80	221 (56.3)	56 (57.7)	0.81
Female	26 (40.0)	2 (33.3)	0.74	145 (44.3)	39 (42.8)	0.81	171 (43.6)	41 (42.2)	0.81
Underlying comorbidities (n, %)									
Cardiovascular disease	2 (3.07)	0	0.66	32 (9.78)	6 (6.59)	0.35	34 (8.67)	6 (6.18)	0.42
Diabetes mellitus	0	0	-	17 (5.19)	2 (2.19)	0.22	17 (4.33)	2 (2.06)	0.30
Gastrointestinal pathology	2 (3.07)	0	0.66	24 (7.33)	6 (6.59)	0.81	26 (6.63)	6 (6.18)	0.99
Hematologic malignancy	0	0	-	12 (3.66)	6 (6.59)	0.22	12 (3.06)	6 (6.18)	0.14
Liver disease (acute or chronic)	7 (10.7)	0	0.40	30 (9.17)	4 (4.39)	0.13	37 (9.43)	4 (4.12)	0.09
Oral cavity	3 (4.61)	0	0.59	10 (3.05)	0	0.09	13 (3.31)	0	0.001
Respiratory dysfunction	6 (9.23)	4 (66.6)	0.001	52 (15.9)	27 (29.6)	< 0.001	58 (14.7)	31 (31.9)	< 0.001
Septic shock	15 (23.0)	1 (16.6)	0.72	98 (29.9)	4 (4.39)	< 0.001	113 (28.8)	5 (5.15)	< 0.001
Solid tumor	10 (15.3)	3 (50.0)	0.04	8 (2.44)	0	0.13	18 (4.59)	3 (3.09)	0.51
Surgery	0	0	-	14 (4.28)	4 (4.39)	0.96	14 (14.7)	4 (4.12)	0.80
Pulmonary diseases	17 (26.1)	3 (50.0)	0.21	50 (15.2)	17 (18.6)	0.44	67 (17.0)	20 (20.6)	0.21
Tuberculosis	1 (1.53)	0	0.76	24 (7.33)	8 (8.79)	0.65	25 (6.37)	8 (8.24)	0.51
Neurological diseases	10 (15.3)	2 (33.3)	0.26	6 (1.83)	2 (2.19)	0.82	16 (4.08)	4 (4.12)	0.99
UTI	2 (3.07)	2 (33.3)	0.002	12 (3.66)	2 (2.19)	0.49	14 (3.57)	4 (4.12)	0.79
Risk factors									
Previous therapy with antibiotics	65 (100)	6 (100)	0.99	103 (31.4)	32 (35.1)	0.51	168 (42.8)	38 (39.1)	0.51
Treatment with antifungal agents	35 (53.8)	6 (100)	0.59	78 (23.8)	24 (26.3)	0.46	113 (28.8)	30 (30.9)	0.68
Central venous catheter	2 (3.07)	0	0.66	34 (10.3)	16 (17.5)	0.04	36 (9.18)	16 (16.4)	0.04
Urinary tract catheter	4 (6.15)	1 (16.6)	0.34	108 (33.0)	19 (20.8)	0.03	112 (28.5)	20 (20.6)	0.11
Total parenteral nutrition	1 (1.53)	1 (16.6)	0.03	28 (8.56)	8 (8.79)	0.95	29 (7.39)	9 (9.27)	0.54
ICU/PICU/NICU	65 (100)	6 (100)	> 0.99	64 (19.5)	18 (19.7)	0.96	129 (32.9)	24 (24.7)	0.96
Malnutrition	14 (21.5)	2 (33.3)	0.51	28 (8.56)	7 (7.69)	0.79	42 (10.7)	9 (9.27)	0.71
Mechanical ventilation	6 (9.23)	2 (33.3)	0.10	62 (18.9)	32 (35.1)	0.002	68 (17.3)	34 (35.0)	0.004
Laboratory findings									
Anaemia	11 (16.9)	0	0.27	16 (4.89)	2 (2.19)	0.26	27 (6.88)	2 (2.06)	0.07
Thrombocytopaenia	21 (32.3)	1 (16.6)	0.43	52 (15.9)	6 (6.59)	0.02	73 (18.6)	7 (7.21)	0.007
Renal failure	5 (7.69)	2 (33.3)	0.04	20 (6.11)	8 (8.79)	0.37	25 (6.37)	10 (10.3)	0.18
Hyponatraemia	7 (10.7)	0	0.40	28 (8.56)	7 (7.69)	0.79	35 (8.92)	7 (7.21)	0.59
Hypernatremia	11 (16.9)	0	0.27	8 (2.44)	0	0.13	19 (4.84)	0	0.03

Table 4. Factors associated with 30-days mortality by univariate analysis in inpatients with candidaemia.

Variables	*Patients (50–98 years)* **Odd ratio 95% Confidence interval *p*-value**		*All patients* **Odd ratio 95% Confidence interval *p*-value**	
Respiratory dysfunction	2.758 0.8068 to 4.747	< 0.001	2.705 1.649 to 4.433	< 0.001
Pulmonary diseases	2.337 1.371 to 3.942	0.42	2.172 1.332 to 3.622	0.46
Central venous catheter	1.970 1.000 to 3.654	0.04	1.953 0.5168 to 3.694	0.04
Urinary tract catheter	0.5351 0.3101 to 0.9242	0.03	- -	-
Septic shock	0.1074 0.04112 to 0.2920	< 0.001	0.1342 0.05736 to 0.3194	< 0.001
Mechanical ventilation	2.186 1.312 to 3.582	0.003	2.056 1.249 to 3.387	0.006
Thrombocytopaenia	0.3733 0.1662 to 0.8667	0.02	0.3399 0.1476 to 0.7456	0.005
Renal failure	1.480 0.6648 to 3.449	0.35	- -	-

Table 5. Factors associated with 30-days mortality by multivariate analysis.

Antifungal agents	MIC/MEC ranges[a]	MIC50/MEC50	MIC90/,MEC90	GM	S/WT (%)	SDD/I (%)	*R*/NWT (%)
C. albicans							
AMB (1640)	≤ 0.05 to 8	0.25	2	0.46	1449 (100)	-	-
FC (1679)	≤ 0.03 to 4	0.5	2	0.49	1629 (97.0)	-	50 (2.97)
FCA (1599)	≤ 0.06 to > 64	0.25	4	0.37	1347 (84.2)	61 (3.81)	191 (11.9)
ITR (1880)	≤ 0.06 to > 32	0.25	1	0.34	1356 (72.1)	-	524 (27.8)
VRC (2271)	0.015 to > 32	0.12	0.5	0.12	1787 (91.6)	99 (5.07)	385 (19.7)
C. tropicalis							
AMB (654)	≤ 0.06 to 8	0.25	1	0.35	748 (99.2)	-	6 (0.79)
FC (664)	≤ 0.03 to > 8	0.06	0.25	0.80	622 (93.6)	-	42 (6.75)
FCA (463)	≤ 0.12 to > 128	1	> 8	1.45	441 (95.2)	5 (1.07)	17 (3.67)
ITR (256)	≤ 0.12 to > 16	1	4	0.94	252 (98.8)	-	4 (1.12)
VRC (750')	0.015 to > 32	0.125	1	0.44	735 (98.0)	6 (0.80)	9 (1.20)
C. glabrata							
AMB (306)	≤ 0.015 to 4	0.125	0.5	0.17	303 (99.0)	-	3 (0.98)
FC (406)	≤ 0.015 to > 8	0.125	0.5	0.18	406 (100)	-	-
FCA (206)	≤ 0.5 to > 256	0.5	4	0.22	185 (89.8)	8 (3.88)	13 (6.31)
ITR (391)	≤ 0.12 to > 16	0.12	1	0.82	336 (85.9)	-	55 (14.0)
VRC (506)	0.015 to > 32	0.25	1	0.36	494 (88.6%)	-	12 (11.3%)
C. parapsilosis							
AMB (159)	≤ 0.015to 4	0.125	1	0.18	157 (98.7)	-	2 (1.25)
FC (259)	≤ 0.12 to > 16	0.5	4	1.26	259 (100%)	-	-
FCA (224)	≤ 0.5 to > 256	8	64	0.86	167 (74.5)	8 (3.57)	49 (21.8)
ITR (141)	≤ 0.12 to > 16	1	4	1.21	98 (69.5)	-	43 (30.4)
VRC (75)	0.015 to > 32	0.25	2	0.26	161(73.1)	23 (10.4)	36 (16.3)
C. krusei							
AMB (104)	≤ 0.015 to 4	0.125	0.5	0.10	101 (97.2)	-	3 (2.88)
FC (134)	≤ 0.12 to > 8	0.5	1	0.61	127 (94.7)	-	7 (5.22)
FCA	≤ 0.5 to > 256	-	-	-	-	-	-
ITR (94)	≤ 0.12 to > 16	1	2	1.41	84 (89.3)	-	10 (10.6)
VRC (124)	0.015 to > 32	0.25	8	0.87	121 (97.5)	3 (2.4)	-
Otther[b]							
AMB (109)	≤ 0.03 to 1	0.125	0.5	2.14	109 (100%)	-	-
FC (59)	≤ 0.06 to > 1	0.125	0.5	0.19	59 (100%)	-	-
FCA (59)	≤ 0.5 to > 8	1	8	0.19	40 (67.7%)	15 (25.4%)	4 (6.77%)
ITR (59)	≤ 0.03 to > 2	0.5	1	0.22	45 (76.2%)	-	14 (23.7%)
VRC (37)	0.06 to > 1	0.125	1	0.18	32 (88.8%)	-	5 (13.8%)

Table 6. Antifungal susceptibility profiles of *Candida* isolates. Abbreviations: MIC = Minimum inhibitory concentration, MEC = Minimum effective concentration, GM = Geometric mean, ECV = Epidemiological cutoff values, WT = Wild types, NWT = non-wild types. a For all drugs, b; *C. lusitaniae*; *C. metapsilosis* ; *C. norvegensis*.

our study[18,43–51]. Reports from countries and regions such Iran, Korea, Indonesia, North America, Southern Europe, eastern China, southwestern China, northeastern China, and northern Taiwan, have consistently reported a significant prevalence of *C. tropicalis* among candidemia patients[20,52–62]. The regional variation in *Candida* species prevalence in candidemia may be due to differences in climate, healthcare practices, antifungal use, patient demographics, diagnostic capabilities, hygiene practices, or globalization. These factors collectively influence species distributions and resistance patterns.

Candida infections were slightly more common in males than in females. Similar population distributions have been reported in other studies in China[63]. Conversely, studies from Ethiopia have reported a higher number of *Candida* infections in women than in men[18,64]. Although the variation in the frequency of candidiasis between men and women may be attributed to anatomical and physiological differences specific to each sex[18,65], the reasons for the high percentage of *Candida* infections in men in China remain unclear. The medical wards documented the highest number of candidemia cases, consistent with a previously published study[20]. However, most studies have reported the highest case numbers in ICUs[66–69]. One possible reason concerns the demographic characteristics of the inpatients in our hospital, most of whom had more than two underlying diseases and were hospitalized in medical wards. However, the incidence of candidemia in ICUs is high in most studies.

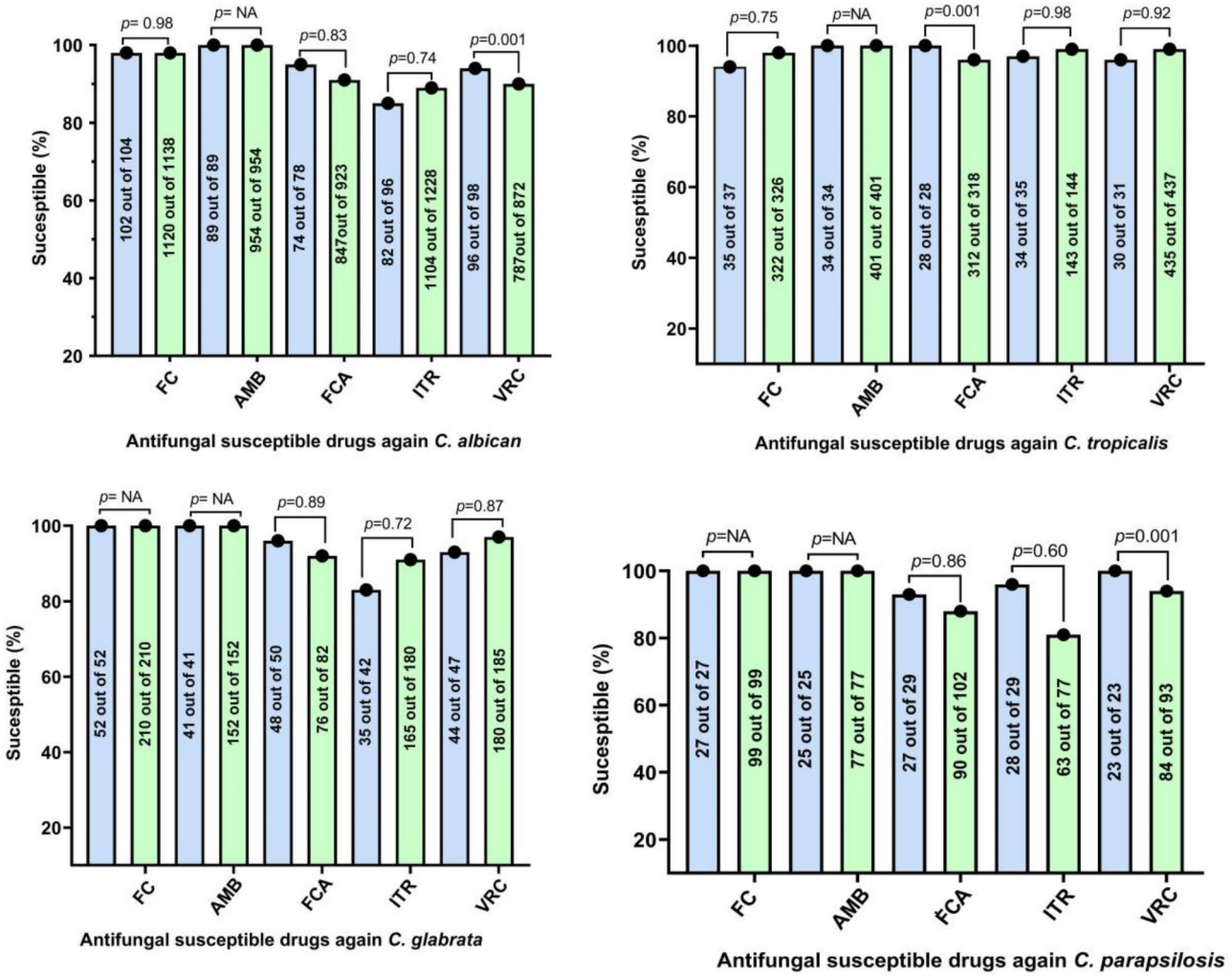

Fig. 2. Differences in the antifungal susceptibility of isolates obtained from cases of candidemia and non-candidemia. The blue bars represent BSCI isolates, while the green bars represent non-BSCI. *P*-values less than 0.05 were considered statistically significant. AmB, amphotericin B; FC, 5-flucytosine; FCA, fluconazole; ITR, itraconazole; VRC, voriconazole; NYS, nystatin.

According to our data, sex ratio, hematologic malignancies, liver disease (acute or chronic), malnutrition, mechanical ventilation, skin barriers, surgery, tuberculosis, neurological diseases, UTIs, central venous catheters, anemia, renal failure, hyponatremia, hypernatremia, and seven-day and total mortality rate were not significantly different between pediatric and adult patients. Oral cavities were the only underlying comorbidity more frequent in pediatric than in adult patients. Underlying comorbidities, including cardiovascular disease, diabetes mellitus, gastrointestinal pathology, respiratory dysfunction, and pulmonary diseases, were more frequent in adult patients than pediatric patients. Several other studies from China have also reported candidemia patients with comorbidities[20,21,70].

A central venous catheter, septic shock, and ICU admission were more common risk factors in adult patients than in pediatric patients (Table 3). The prevalence of *Candida* species on the skin of the hands and the ability to transfer to catheters are widely recognized[71,72]. The present findings suggest that healthcare personnel may contribute to the prevalence of various forms of invasive candidiasis through horizontal transmission of *Candida* species. Laboratory findings showed that only thrombocytopenia was in a higher proportion in adult patients compared to pediatric patients. Previous studies have identified thrombocytopenia as an independent risk factor for death in patients with candidemia[28].

The 30-day mortality rate between pediatric and adult patients was dissimilar to the values from previous reports in China[18]. The univariate predictors of outcomes indicated pediatric patients had only three significant predictors. The adult patients had eight significant predictors, including respiratory dysfunction and septic shock, similar to a previous study from southwest China. The predictors for outcome included a central venous catheter, mechanical ventilation, thrombocytopenia, and a urinary tract catheter (Table 4). However, further epidemiological research is needed for confirmation, as other studies have not reached firm conclusions.

We compared the susceptibility profiles of *Candida* isolates obtained from BSCI and non-BSCI (Fig. 2). For *C. albicans*, the obtained isolates from BSCI were relatively more susceptible to all drugs than non-BSCI except for ITR. However, for *C. albicans*, the susceptibility profile to azole was similar to that in previous reports from China[18]. *C. parapsilosis* and *C. tropicalis* exhibited high susceptibility to the drugs VRC and FCA in BSCI compared to non-BSCI. Similarly, *C. glabrata* and *C. krusei* demonstrated lower susceptibility to azole in BSCI compared to non-BSCI. The continued recommendation of empirical prophylactic treatments by prescribers may be the cause of the lowered susceptibilities of the NCA-causing candidemia isolates.

The study has several limitations. The results may not apply to all patients with invasive candidiasis or to other institutions, as this was a retrospective study conducted at a single hospital. The distribution and prevalence of candidiasis or candidemia can vary widely depending on the institution. Unfortunately, our hospital did not have any data on echinocandins because of the clinical microbiology laboratory's technical limitations and the impact of hospital policies. However, the study's epidemiological findings can help develop strategies for improving the hospital's management of invasive candidiasis.

Conclusion

This study identified the epidemiological patterns and incidence of candidiasis, especially candidemia, in a developing region of China. In this study, we reported the distribution, risk factors, and susceptibility to antifungal agents of *Candida* infections. *C. tropicalis* was more prevalent than *C. glabrata* in patients with candidemia. Respiratory dysfunction, pulmonary diseases, septic shock, and thrombocytopenia were independent risk factors for 30-day mortality. Regarding bloodstream infections compared with non-bloodstream infections (non-BSCI), AMB was effective (100%) against all tested isolates. The epidemiological findings of the study are valuable for developing strategies to improve hospital management and control of candidiasis.

Data availability

All the data are presented in the manuscript; any raw data can be available by request to the first author (email; sabir_khan182@yahoo.com).

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Author contributions
Conceptualization, Y.Z; and S.K; methodology, S.K; L.C; and Y.Z; software, S.K; and H.B; validation, M.N.K; B.H; and W.F; formal analysis, Q.W; and B.H; investigation, H.B; and D.Z; resources, Y.Z; and L.C; data curation, F.Y; X.W; and L.C; writing—original draft preparation, S.K.; writing—review and editing, S.K., and M.N.K; visualization, J.W; C.M; and L.L; supervision, Y.Z; project administration, L.C; and Y.Z; All authors have read and agreed to the published version of the manuscript.

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Declarations

Ethics approval and consent to participate
Ethical approval was provided by the Second Affiliated Hospital of Shantou University Medical College, Shantou, Human Research Ethics Committee (Ref; 2022 – 167) following the Declaration of Helsinki criteria. The ethical committee waived consent forms from the patients as all the clinical samples were obtained from the Second Affiliated Hospital of Shantou University Medical College, hospital laboratory as routine work and not for this study.

Competing interests
The authors declare no competing interests.

Informed consent
Statement.
Patient consent was waived as we get data from the Second Affiliated Hospital of Shantou University Medical College, Shantou, surveillance system as a secondary source; no patient image or figure is involved.

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Correspondence and requests for materials should be addressed to Y.Z.

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