A seven-year surveillance study of the epidemiology, antifungal susceptibility, risk factors and mortality of candidaemia among paediatric and adult inpatients in a tertiary teaching hospital in China

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Research

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Abstract

Background There are no current national estimates of the candidaemia burden in China, and epidemiological candidaemia data from the underdeveloped region of China are lacking.

Methods A 7-year retrospective study was carried out to analyse the prevalence, species distribution, antifungal susceptibility, risk factors and inpatient mortality of candidaemia among paediatric and adult patients in a regional tertiary teaching hospital in China.

Results During the seven-year study period, a total of 201 inpatients with candidaemia were identified. The median age of the patients was 65 years (range, 1 day to 92 years), and 114 of the patients (56.7%) were male; the mean annual incidence was 0.26 cases per 1,000 admissions (0.42 cases per 1,000 paediatric vs 0.24 cases per 1,000 adult admissions, P<0.05). Candida albicans was the most common fungal species (81/201, 40.3%) in all patients, Candida glabrata was the most common fungal species (18/35, 51.4%) in paediatric patients. Most isolates were susceptible to flucytosine (99.0%) and amphotericin B (99.0%), and the activity of antifungal agents against Candida species was no significant difference in satisfaction between paediatric and adult patients(P>0.05). The all-cause mortality rate was 20.4% (paediatric patients: 11.4% vs adult patients:22.3%, P>0.05). The univariate predictors of poor outcomes in paediatric patients were less than that in adult patients (4 vs 11 predictors). Respiratory dysfunction and septic shock were independent predictors of 30-day mortality in all patients.

Conclusions The epidemiological data of candidaemia in paediatric and adult patients are only different in the distribution of Candida species and the mean annual incidence of candidaemia. Flucytosine and amphotericin B could be used as the first-choice agent when there is no the result of antifungal susceptibility tests.

Background Candidaemia is the most common fungal disease among hospitalized patients worldwide and is the fourth to tenth most common bloodstream infection (BSI) in most population-based studies[1, 2]. It is associated with significant morbidity and mortality[3]. The main risk factors for candidaemia include critical illness, a long intensive care unit (ICU) length of stay, haematologic malignant disease, solid-organ transplantation, solid-organ tumours, low birth weight in neonates and preterm infants, broad-spectrum antimicrobial agent use, central venous catheterization (CVC), total parenteral nutrition, haemodialysis, abdominal surgery, and aggressive chemotherapy[1]. With the increase in related research, reports have shown that the incidence of candidaemia is age-specific, with maximum rates observed in those with older age (over 65 years)[1, 4, 5].

More than 40 Candida species can cause candidaemia in humans[6]. Five species of Candida (Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis and Candida krusei) are the most common species and account for more than 90% of all the isolates[2]. The variability in the relative proportions of Candida isolates has been associated with clinical condition or risk factors such as age, underlying comorbidities, the extensive use of antifungal agents and geography. Candida albicans is the primary cause of candidaemia and one of the most common species in many countries, Candida glabrata is the second or third most common species in the USA and Europe, and Candida parapsilosis is predominant in neonates in South America, southern Europe and Asia[2]. The global incidence of candidaemia varies from 0.3 to 5 per 1,000 admissions according to geographical region, local epidemiology, age and other factors[7]; the 30-day mortality among all patients with candidaemia has been reported to be between 22% and 70%[8], and the cost of candidaemia has been reported to be US $40,000 per patient[1, 9, 10].

In China, the epidemiology of candidaemia varies widely among different areas[11]. Epidemiological surveillance of candidaemia has focused on ICUs and single centres in China, and national surveillance systems are usually absent. Most of
the existing epidemiological surveillance of candidaemia has focused on adults or children, and little information about
general populations (including neonates, children and adults) is known. Therefore, in the present study, we performed a seven-
year retrospective study to evaluate the epidemiology, antifungal susceptibility, risk factors and mortality of candidaemia
among all inpatients in a tertiary teaching hospital in China.

Methods

Patient data collection

We conducted a retrospective observational study of electronic laboratory records. The fungal specimen data were collected
from inpatients with candidaemia in the Affiliated Hospital of Southwest Medical University (Luzhou, China), which is a 3,200-
bed tertiary care teaching hospital with 43 wards and approximately 120,000 annual admissions, from January 2013 to
December 2019. The diagnostic criteria of candidaemia were based on the guidelines for the diagnosis and treatment of Candidiasis: the expert consensus issued by the Chinese Medical Association[12]; these criteria were also in accordance with
the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)* guidelines for the diagnosis and
management of Candida diseases 2012[13, 14] and the Infectious Diseases Society of America (IDSA) Guidelines for the
Management of Candidiasis: 2016 Update[15]. For each patient, only the first episode was included in our analysis. Patient
cultures with two or more Candida species were excluded from the analysis, and all data were collected from electronic
medical records. The following data were retrospectively collected from all patients: demographic characteristics, underlying
comorbidities, Candida species, susceptibility to antifungal agents and mortality. Data on the following risk factors
associated with candidaemia were also collected: gestational age and weight of neonates, indwelling central vascular
catheter, mechanical ventilation, systemic corticosteroid treatment (a dose equivalent to prednisone 10 mg/d for at least 14
days), total parenteral nutrition, chemotherapy, abdominal surgery, ICU admission, neutropenia (absolute neutrophil count
<500 cells/μl), concomitant bacterial infections, septic shock, haemodialysis, broad-spectrum antibiotic use and treatment
with antifungal agents. The study protocol was approved by the ethics committee of the hospital (Project No. K2016004). The
need for informed consent was waived by the Clinical Research Ethics Committee.

Microorganism identification and antifungal susceptibility

According to the manufacturer's instructions, blood was inoculated into both aerobic and anaerobic BacT/AlerT 3D vials
(Bruker Diagnostics Inc., USA). All positive cultures were manually sampled and inoculated onto CHROMagar Candida
medium (CHROMagar Company, France) to ensure viability and purity. The identification of all species was confirmed by a
MicroScan WalkAway 96 Plus System (Siemens, Germany) and Microflex LT (Bruker Diagnostics Inc., USA) matrix-assisted
laser-desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) system.

Antifungal susceptibility tests for fluconazole (FCA), itraconazole (ITR), voriconazole (VRC), flucytosine (5-FC) and
amphotericin B (AMB) were performed for all Candida strain isolates by using an ATB FUNGUS 3 kit (bioMérieux, France). The
minimal inhibitory concentrations (MICs) of the antifungal agents were judged by visualization in our laboratory according to
the manufacturer's instructions. The quality control strains were C. parapsilosis ATCC 22019 and C. krusei ATCC 6258. The
results were interpreted using the Clinical and Laboratory Standards Institute M27-A3 microbroth dilution method.

Statistical analyses

The data were analysed using Microsoft Excel (version 2016, Redmond, USA) and IBM SPSS software version 24 for Windows
(IBM, Armonk, USA). The categorical data were compared using chi-square or Fisher's exact tests. The continuous data were
analysed using Student’s t-test or Mann-Whitney U test. Multivariable logistic regression analysis was performed to identify
independent predictors of candidemia and 30-day hospital mortality. Biologically plausible variables with a value of P<0.1
according to the univariate analyses were included in the multiple logistic regression model. Statistical significance was determined using two-tailed tests, and P<0.05 was considered statistically significant.

Results

A total of 201 distinct candidaemia episodes were identified during our study period. The median age was 65 years (range 1 day -92 years), and 114 patients (56.7%) were male. Most candidaemia episodes were diagnosed in medical wards (89, 44.3%), followed by ICUs (46, 22.9%), paediatric wards (35, 17.4%) and surgical wards (31, 15.4%). Most of the patients had one or more comorbidities. Pulmonary infection (49.8%), chronic/acute renal failure (45.3%) and cardiovascular disease (42.8%) were the most common underlying comorbidities, followed by neurological diseases (38.8%), diabetes mellitus (29.9%), respiratory dysfunction (28.9%), gastrointestinal pathologies (28.9%) and chronic/acute liver disease (24.4%). Moreover, the most common underlying conditions documented prior to candidaemia were prior exposure to broad-spectrum antibiotics (89.1%), treatment with antifungal agents (56.7%), concomitant bacterial infections (54.7), total parenteral nutrition (47.3%), mechanical ventilation (43.3%), ICU/paediatric ICU (PICU)/neonatal ICU (NICU) admission (40.3%) and CVC (38.3%). In total, 53 (26.4%, 53/201) patients had received previous antifungal treatment, and paediatric patients accounted for 71.4% (25/35) of the total. The underlying comorbidities in adult patients were significantly worse than those in paediatric patients, but the number of underlying conditions in paediatric patients were significantly higher than those in adult patients, and the difference was statistically significant (P<0.05). FCA was the most frequently used empirical antifungal treatment (60/114, 52.6%). The demographic and clinical characteristics of the patients are summarized in Table 1 and Table 2.

The mean annual incidence of candidaemia was 0.26/1,000 admissions, including 0.42/1,000 paediatric admissions (1.61/1,000 neonatal admissions (<28 days), 0.06/1,000 infant admissions (28 days-1 year) and 0.04/1,000 child admissions (1 year < age < 16 years)) and 0.24/1000 adult admissions (0.09/1,000 surgical admissions, 0.30/1,000 medical admissions and 1.64/1,000 ICU admissions). According to the Candida species, the incidence of the three most commonly isolated Candida species were as follows: *C. albicans*, 0.10/1,000 admissions; *C. glabrata*, 0.09/1,000 admissions; and *C. tropicalis*, 0.04/1,000 admissions.

The most common species among all Candida species isolates was *C. albicans* (40.3%), followed by *C. glabrata* (36.3%), *C. tropicalis* (13.9%), *C. parapsilosis* (4.0%), *C. krusei* (3.0%) and others (2.5%). The distribution of Candida species in paediatric (<16 years) and adult (≥16 years) patients is shown in Table 1. In patients aged 0-16 years and 49-65 years, *C. glabrata* was the predominant species (51.4% and 41.1%, respectively), but in patients aged 17-49 and >65 years, *C. albicans* was the main species (45.7% and 56.9%, respectively). The distribution of Candida species in paediatric, surgical, internal medicine and ICU wards is shown in figure 1.

The results of *in vitro* susceptibility testing of Candida strain isolates are summarized in Table 3. All isolates were highly susceptible to AMB (99.0%) and 5-FC (99.0%). The resistance rates of ITR, VRC and FCA were 24.9% 19.4% and 18.5%, respectively. *C. tropicalis* had the highest antifungal agent resistance rate among the Candida species and was resistant to FCA (39.3%), ITR (39.3%) and VRC (42.9%). The activity of antifungal agents against Candida species was no significant difference in satisfaction between paediatric and adult patients (P>0.05). The detailed data are shown in Table 3.

The all-cause mortality rate in the 201 patients was 20.4% (41/201). The 7-day and 30-day mortality rates were 8.5% (17/201) and 17.9% (36/201), respectively. The mortality rates of *C. albicans*, *C. glabrata*, *C. tropicalis* and *C. parapsilosis* infections were 27.2% (22/81), 16.4% (12/73), 21.4% (6/28) and 12.5% (1/8), respectively. The mortality rates for paediatric wards,
medical wards, surgical wards and ICU wards were 11.4% (4/35), 22.5% (20/89), 16.1% (5/31) and 26.1% (12/46), respectively. The mortality rates for different age groups were 11.4% (4/35, 0-16 years) in paediatric patients and 22.3% (37/166>16years), 7.7% (4/52, 17-49 years), 19.6% (11/56, 50-65 years) and 37.9% (22/58, >65 years)) in adult patients.

The univariate predictors of poor outcomes due to candidaemia are shown in Table 4. For paediatric patients with candidaemia, the variables associated with 30-day mortality were as follows: length of hospital stay, respiratory dysfunction, chronic/acute renal failure and septic shock. For adult patients with candidaemia, the variables associated with 30-day mortality were as follows: age, length of hospital stay, respiratory dysfunction, pulmonary infection, cardiovascular disease, chronic/acute renal failure, other invasive catheters, mechanical ventilation, septic shock, C. albicans infection, concomitant bacterial infection and haematologic (nonmalignant) disease. The results of the multivariate analysis are listed in Table 5. Because the total number of paediatric patients (35 patients) and deaths (3 patients) were very small, multivariable logistic regression analysis was not performed in paediatric patients. Respiratory dysfunction and septic shock were independent predictors of 30-day mortality in all patients and adult patients. The length of hospital stay was a protective factor for 30-day mortality in all patients and adult patients, and other invasive catheters were only the protective factor for 30-day mortality in all patients.

Discussion

This was a 7-year retrospective study of candidaemia in a regional tertiary teaching hospital in Southwest China. We not only analysed the epidemiological characteristics, including the basic information of patients, underlying comorbidities, risk factors, distribution of Candida species, antifungal agent use, antifungal agent susceptibility results and patient outcomes, but also made epidemiologically compared paediatric patients and adult patients.

Our data showed that there was no significant difference in the sex ratio, length of hospital stay or mortality between adult and paediatric patients (P>0.05). However, the proportions of underlying comorbidities in paediatric patients, including pulmonary infection, neurological diseases, congenital malformations/syndromes and haematologic (nonmalignant) disease, were higher than those in adult patients (P<0.05), and the other proportions in adult patients were similar or higher than those in paediatric patients (Table 2). There were differences in the type and number of underlying comorbidities between paediatric patients and adult patients, and the low proportion of underlying comorbidities in paediatric patients is similar to the results of other studies on paediatric candidaemia. Among the risk factors, only CVC, other invasive catheters and abdominal surgery in adult patients had higher risks than those in paediatric patients (P<0.05), and other risk factors in children had higher or similar risks as those in adult patients (Table 2). The univariate predictors of poor outcomes in paediatric patients with candidaemia were only four predictors, which was significantly less than that in adults patients (11 predictors) (Table 4). This situation has not been clearly shown in other studies, and more epidemiological investigations are needed to confirm it. The incidence of candidaemia in pediatric patients was significantly higher than that in adults (P<0.05) (Table 2), however, there was no significant difference in mortality between pediatric patients and adult patients (P>0.05) (Table 2), it is different from other studies[16, 17].

Our data showed that the median age of patients with candidaemia and the proportion of males were similar to those in other studies[8, 18-23]. Moreover, our study showed that the patients with candidaemia were hospitalized mostly in internal medicine wards, which was different from other studies that reported hospitalisation in mainly ICU wards[8, 22, 24-27], and similar to other studies[28-31]. This phenomenon may be related to the demographic characteristics of the inpatients in our hospital, most of whom had more than two underlying diseases and were hospitalized in internal medicine wards. However, the incidence of candidaemia was still the highest in the ICU, similar to other studies[8, 30-34]. In accordance with other
studies[17-19, 24, 25, 30, 32, 35, 36]. *C. albicans* was the most common cause of candidaemia in the whole hospital, but the proportion of non-*C. albicans* infections was higher than that of *C. albicans* infections. Moreover, the proportions of *C. glabrata* in surgical, internal medicine and paediatric wards were the highest, which was different from other studies in China[18, 19, 35-37] and similar to other studies in other countries[4, 22, 27, 29, 32]. This may be due to the large number of elderly patients and the increasing use of azole antifungal agents.

Our data showed that the incidence of candidaemia increased from 0.20 episodes/1,000 admissions in 2013 to 0.37 episodes in 2016 and then dropped to 0.26 between 2017 and 2019. The change in the annual incidence rate was mainly due to the change in the incidence rate in paediatric patients. The reasons may be due to the gradual easing of restrictions of China's two-child policy since 2013. The number of geriatric pregnant women has increased annually, resulting in an increase in the incidence of neonatal diseases. The change trend was similar to that reported by Oeser et al[38]. The overall morbidity and 30-day mortality in ICUs and hospitals in this study were similar to those in another hospital in this region of China[18], but lower than those in hospitals in other regions of China[35, 37] and other countries[5, 8, 16, 20, 21, 23, 25, 30]. It has been reported that the overall mortality rate of candidaemia is 20%-49% globally[39], and the mortality rate was 20.4% in our hospital, which is low compared to global rate. This may be because the demographic characteristics and underlying diseases of patients in this region are different from those in other regions or countries, and few severe patients were admitted to our hospital.

With regard to resistance, resistance to FCA, ITR and VRC were common in *C. albicans* and non-*C. albicans* species (Table 3). In our study, AMB and 5-FC were highly active against all Candida species. In paediatric patients, the resistance rate of ITR was higher than that in adult patients, but the resistance rates of FCA and VRC were lower than those in adult patients; however, and the resistance rate of Candida species was no significant difference in satisfaction between paediatric and adult patients(P>0.05). Moreover, FCA was highly active against all Candida species in paediatric patients and could be used in paediatric patients with candidaemia as a first-line agent. In the whole hospital, the resistance rate to azole was higher than those reported in other regions[18, 19, 36] and countries[17, 19, 25, 29, 30, 34]. This may be related to the long-term use of empirical prophylactic drugs by clinicians. Therefore, it was necessary to conduct an epidemiological analysis of antifungal agent susceptibility and guide clinicians to choose the rational antifungal agents to avoid the continuous increase in resistance rates.

In this study, we analysed the prognostic factors in all patients and adult patients with candidaemia. Age, length of hospital stay, respiratory dysfunction, pulmonary infection, cardiovascular disease, chronic/acute renal failure, other invasive catheters, mechanical ventilation and septic shock were the common predictors of mortality in the univariate analysis (P<0.05) in both adult patients and all patients, and the univariate predictors of poor outcomes in paediatric patients were less than that in adults patients (4 vs 11 predictors), as shown in Table 4. Because the total number of paediatric patients (35 patients) and deaths (3 patients) were very small, multivariable logistic regression analysis was not performed in paediatric patients. However, our study showed that respiratory dysfunction and septic shock were common independent predictors of 30-day mortality in both adult patients and all patients, and length of hospital stay and other invasive catheters were protective factors for 30-day mortality in all patients. The prognostic factors of 30-day mortality in all patients and adult patients were almost the same, and the independent predictors were the same; there were no significant differences. Septic shock was an independent predictor of 30-day mortality; this has been reported in many other studies[18, 35]. However, the other factors reported here have rarely been reported in other studies[35, 40-43], possibly because the demographic characteristics, underlying diseases and risk factors of the patients in our study were different from those in other studies; this may be the reason that the independent predictors and protective factors in this study were different from those in other studies[5, 35, 40-43]. The independent predictors and protective factors in different regions and countries are shown in Table 6.
This study has several potential limitations. First, due to the technical limitations of the clinical microbiology laboratory and the impact of hospital policies, there are were data on echinocandins in our hospital. Second, this was a single-centre retrospective study. Our data might be influenced by the distribution of the regional population, the level of medical intervention, and the distribution of patient types. Therefore, the results may not be generalizable to all patients with candidaemia in China. The epidemiological findings will pave the way for more in-depth studies and help us establish better antifungal stewardship in our hospital.

**Conclusion**

*C. albicans* was the main Candida species, but *C. glabrata* has become the second most common species in this region. FCA was the main antifungal agent for paediatric patients. AMB and 5-FC were highly active against all Candida species. The morbidity and mortality rates in elderly patients were the highest. Respiratory dysfunction and septic shock were independent predictors of 30-day mortality. Further multi-centre studies on candidaemia in different geographical regions in all patients should be conducted to help infection specialists assess the distribution and trends in patients with suspected fungal infections.

**Abbreviations**

BSI: bloodstream infection; ICU: intensive care unit; PICU: paediatric intensive care unit; NICU neonatal intensive care unit; USA: United States of America; ATCC: American type culture collection; MALDI-TOF MS: Matrix-assisted laser desorption/ionization-time of flight mass spectroscopy; FCA: fluconazole; ITR: itraconazole; AMB: amphotericin B; VRC: voriconazole; 5-FC: flucytosine; CVC: central venous catheter; MIC: minimal inhibitory concentration; OR: odds ratio; CI: confidence interval.

**Declarations**

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**Availability of data and materials**

The data set supporting the conclusions in this article is available from the corresponding author on reasonable request.

**Authors’ contributions**

ZRZ, GT and JD designed the study and drafted the manuscript. ZRZ, YHD, KY, JBL, GRL and JD collected the data. ZRZ and GT analyzed the data; ZRZ and GT wrote the paper. ZRZ and GT are contributed equally to this work and share first authorship. All authors have read approved the final manuscript.

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**Ethics approval and consent to participate**

The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (project no. KY2020043). This is a retrospective study. The need for informed consent was waived by the Clinical Research Ethics Committee.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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Tables

Table 1: Distribution and incidence of Candida species.
### Candida species

|              | Total  | C. albicans (n=81) | C. glabrata (n=73) | C. tropicalis (n=28) | C. parapsilosis (n=8) | C. krusei (n=6) | others (n=5) |
|--------------|--------|--------------------|--------------------|----------------------|-----------------------|----------------|-------------|
| **Distribution n(%)** | 100.0% | 40.3%              | 36.3%              | 13.9%                | 4.0%                  | 3.0%           | 2.5%        |
| Paediatric patients (≤16 years) |        |                    |                    |                      |                       |                |             |
| 0-28 days    | 32(15.9) | 16(50.0)           | 15(46.9)           | 0 (0)                | 0 (0)                 | 0 (0)          | 1 (2.9)     |
| 29 days - 1 year | 1(0.5)  | 0 (0)              | 1(100.0)           | 0 (0)                | 0 (0)                 | 0 (0)          | 0 (0)       |
| 2-16 years   | 2(1.0)  | 0 (0)              | 2(100.0)           | 0 (0)                | 0 (0)                 | 0 (0)          | 0 (0)       |
| Adult patients (>16 years) | 166(82.6) | 65(39.2)           | 55(33.1)           | 28(16.9)             | 8(4.8)                | 6(3.6)         | 4(2.4)      |
| 17 - 49 years| 52(25.9) | 21(40.4)           | 19 (36.5)          | 7(13.5)              | 1(1.9)                | 3(5.8)         | 1 (1.9)     |
| 50 - 65 years| 56 (27.9) | 11(19.6)           | 23 (41.1)          | 14 (25.0)            | 5(8.9)                | 1(1.8)         | 2 (3.6)     |
| > 65 years   | 58(28.8) | 33(56.9)           | 13(22.4)           | 7(12.1)              | 2(3.4)                | 2(3.4)         | 1(1.7)      |
| **Gender**   |         |                    |                    |                      |                       |                |             |
| Male         | 114(56.7)| 44 (38.6)          | 39 (34.2)          | 19 (16.7)            | 6(5.3)                | 2(1.7)         | 4 (3.5)     |
| Female       | 87 (43.3)| 37 (42.5)          | 34 (39.1)          | 9(10.3)              | 2(2.3)                | 4(4.6)         | 1 (1.1)     |
| **Incidence (episodes/1,000 admissions)** |  |                    |                    |                      |                       |                |             |
| 2013         | 0.20    | 0.06               | 0.12               | 0.01                 | 0.00                  | 0.01           | 0.00        |
| 2014         | 0.22    | 0.09               | 0.10               | 0.03                 | 0.00                  | 0.00           | 0.01        |
| 2015         | 0.27    | 0.10               | 0.12               | 0.02                 | 0.00                  | 0.03           | 0.00        |
| 2016         | 0.37    | 0.23               | 0.10               | 0.04                 | 0.00                  | 0.01           | 0.00        |
| 2017         | 0.32    | 0.10               | 0.14               | 0.07                 | 0.01                  | 0.00           | 0.00        |
| 2018         | 0.16    | 0.06               | 0.07               | 0.02                 | 0.00                  | 0.00           | 0.00        |
| 2019         | 0.26    | 0.08               | 0.04               | 0.05                 | 0.05                  | 0.01           | 0.03        |
| **Mean annual incidence** | 0.26 | 0.10               | 0.09               | 0.04                 | 0.01                  | 0.01           | 0.01        |

*Others include *C. guilliermondii* (4), *C. haemulonii* (1) and *C. inconspicua* (1).
Statistical results of demographic characteristics of pediatric and adult patients

| Age (median range) | All patients (n=201) | Child patients<16 years (n=35) | Adult patients>16 years (n=166) | P* |
|--------------------|----------------------|-------------------------------|-------------------------------|----|
|                    | 65 years (1 day, 92 years) | 1 day (1 day,5 years) | >16 years (92 years) | <0.001 |
| Gender (male:female) | 114:87 | 22:13 | 92:74 | 0.420 |
| Length of hospital stay (days) | 36.9±39.5 | 41.5±20.9 | 30.6±39.6 | 0.117 |
| Underlying comorbidities (n, %) | 24 (11.9) | 2 (5.7) | 22 (13.3) | 0.211 |
| Gastrointestinal perforation | 58 (28.9) | 3 (8.6) | 55 (33.1) | 0.004 |
| Respiratory dysfunction | 100 (49.8) | 24 (68.6) | 76 (45.8) | 0.014 |
| Pulmonary infection | 86 (42.8) | 3 (8.6) | 83 (50.0) | <0.001 |
| Cardiovascular disease | 78 (38.8) | 24(68.6) | 54 (32.5) | <0.001 |
| Neurological diseases | 58 (28.9) | 2 (5.7) | 43 (25.9) | 0.001 |
| Gastrointestinal pathology | 49 (24.4) | 9 (25.7) | 40 (24.1) | 0.839 |
| Chronic/acute liver disease | 91 (45.3) | 9 (25.7) | 82 (49.4) | 0.011 |
| Chronic/acute renal failure | 15 (7.5) | 0 (0) | 15 (9.0) | 0.065 |
| Haematological malignancy | 11 (5.5) | 2 (5.7) | 9 (5.4) | 0.697 |
| Congenital malformations/syndromes | 6 (3.0) | 3 (8.6) | 3 (1.8) | <0.001 |
| Diabetes mellitus | 60 (29.9) | 0 (0) | 60 (36.1) | <0.001 |
| Hematologic (nonmalignant) | 29 (14.4) | 10 (28.6) | 19 (11.4) | 0.009 |
| HIV/AIDS | 10 (5.0) | 0 (0) | 10 (6.0) | 0.136 |
| Severe trauma | 17 (8.5) | 2 (5.7) | 15 (9.0) | 0.521 |
| Risk factors (n, %) | 27 (13.4) | 20 (57.1) | 7 (4.3) | 0.014 |
| Presence of CVC | 60 (29.9) | 5 (14.3) | 55 (33.1) | 0.027 |
| Other invasive catheters | 64 (71.3) | 21 (60.0) | 66 (39.8) | 0.028 |
| Mechanical ventilation | 42 (20.9) | 9 (25.7) | 33 (19.9) | 0.440 |
| Receipt of corticosteroids | 95 (47.3) | 18 (51.4) | 77 (46.4) | 0.587 |
| Total parenteral nutrition | 55 (27.4) | 9 (25.7) | 46 (27.7) | 0.810 |
| Malnutrition | 20 (10.0) | 2 (5.7) | 18 (10.8) | 0.357 |
| Chemotherapy | 30 (16.9) | 0 (0) | 30 (18.1) | 0.006 |
| Hemodialysis | 31 (15.4) | 0 (0) | 31 (18.7) | 0.005 |
| Abdominal surgery | 81 (40.3) | 35 (100.0) | 46 (27.7) | <0.001 |
| ICU/PICU/NICU | 16 (8.0) | 0 (0) | 16 (9.6) | 0.056 |
| Neutropenia | 110 (54.7) | 30 (85.7) | 80 (48.2) | <0.001 |
| Septic shock | 39 (19.4) | 3 (8.6) | 36 (21.7) | 0.075 |
| Broad-spectrum antibiotics | 179 (89.1) | 35 (100.0) | 144 (86.7) | 0.022 |
| Treatment with antifungal agents | 114 (56.7) | 27 (77.1) | 87 (52.4) | 0.007 |
| C. albicans | 73 (36.3) | 18 (51.4) | 55 (33.1) | 0.041 |
| C. glabrata | 28 (13.9) | 0 (0) | 28 (16.9) | 0.009 |
| C. tropicalis | 41 (20.4) | 4 (11.4) | 37 (22.3) | 0.113 |

*Statistical results of demographic characteristics of pediatric and adult patients

a Includes the following diseases: chronic obstructive pulmonary disease and acute respiratory distress syndrome.

b Includes the following diseases: cholecystitis, pancreatitis, and peritonitis.

c Chronic/Acute renal failure is the permanent or sudden and often temporary loss of kidney function with N waste retention a hypourcrinia.
d CVC=central venous catheter.

e a dose equivalent to the prednisone dosage of 0.3 mg/kg/day for at least 14 days.

f including: gastrointestinal perforations, severe acute pancreatitis and complex ventral hernia.

g Neutropenia is the absolute neutrophil count, that is, <500 cells/μl

Table 3 In vitro antifungal susceptibility testing of 201 clinical isolates into 5 antifungal agents

| Species                      | Antifungal agent | Children(35) | Adults(166) | total | Pc |
|------------------------------|------------------|--------------|-------------|-------|----|
|                              |                  | (No of isolates) |            |       |    |
| Candida albicans(81)         | Amphotericin B   | 0            | 0           | 0b    |    |
|                              |                  | 2(12.5)      | 17(26.2)    | 19(23.5) | 0.248 |
|                              |                  | 8(50.0)      | 22(33.8)    | 30(37.0)b | 0.231 |
|                              | Voriconazole     | 4(25.0)      | 20(30.8)    | 24(29.6)b | 0.651 |
| Candida glabrata(73)         | Amphotericin B   | 1(5.6)       | 0           | 1(1.4)b | 0.078 |
|                              |                  | 0            | 0           | 0b    |    |
|                              |                  | 1(5.6)       | 5(9.1)      | 6(8.2) | 0.635 |
|                              |                  | 2(11.1)      | 5(9.1)      | 7(9.6)b | 0.801 |
|                              | Voriconazole     | 1(5.6)       | 2(3.6)      | 3(4.1)b | 0.722 |
| C. tropicalis(28)            | Amphotericin B   | 0            | 1(3.6)      | 1(3.6)b |    |
|                              |                  | 0            | 1(3.6)      | 1(3.6)b |    |
|                              |                  | 0            | 11(39.3)    | 11(39.3)b |    |
|                              |                  | 0            | 11(39.3)    | 11(39.3)b |    |
|                              | Voriconazole     | 0            | 12(42.9)    | 12(42.9)b |    |
| C. parapsilosis(8)           | Amphotericin B   | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
| C. krusei(6)                 | Amphotericin B   | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
| others(5)                    | Amphotericin B   | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
|                              |                  | 0            | 0           | 0     |    |
| All of isolates(201)         | Amphotericin B   | 1(2.9)       | 1(0.6)      | 2(1.0) | 0.222 |
|                              |                  | 0(0)         | 2(1.2)      | 2(1.0) | 0.513 |
|                              |                  | 3(8.6)       | 33(20.6)    | 36(18.5) | 0.096 |
|                              |                  | 10(28.6)     | 40(24.1)    | 50(24.9) | 0.578 |
|                              | Voriconazole     | 5(14.3)      | 34(20.5)    | 39(19.4) | 0.400 |

MIC= minimal inhibitory concentration

Resistance rate was based on the intrinsic resistance of C. krusei and did not follow the actual MICs.

The breakpoints of Candida spp. according to the manufacturer's instructions of ATB FUNGUS 3 system.

The difference of resistance rate between children and adults was analyzed by chi square test.
Table 4. Factors associated with 30-days mortality by univariate analysis in inpatients with candidaemia
| Variable                                      | Adult patients (>16 years) 30-days outcome | P-value | Child patients (0-16 years) 30-days outcome | P-value | All patients 30-days outcome | P-value |
|----------------------------------------------|------------------------------------------|---------|---------------------------------------------|---------|----------------------------|---------|
|                                             | Survived (n=133) Died (n=33)             |         | Survived (n=32) Died (n=3)                  |         | Survived (n=165) Died (n=36) |         |
| **Median age (range)**                       | 60 years (18, 92 years) 67 years (29, 86 years) | 0.001   | 1 days (1 day) 1 days (1 day, 5 years)     | 0.585   | 1 days (1 day) 1 days (1 day, 5 years) | 0.001   |
| Gender (male:female)                         | 72:61                                    | 0.503   | 26:13                                       | 0.164   | 91:74                       | 0.557   |
| **Length of hospital stay (days)**           | 35.3±42.8                                | 0.002   | 43.8±20.2                                   | 0.029   | 36.9±39.5                   | <0.001  |
| Underlying comorbidities (n, %)              |                                          |         |                                             |         |                             |         |
| Gastrointestinal perforation                 | 15(11.3)                                 | 0.132   | 2(6.3)                                      | 0.656   | 17(10.3)                    | 7(19.4)  |
| Respiratory dysfunction                      | 28(21.1)                                 | <0.001  | 1(3.1)                                      | <0.001  | 29(17.6)                    | <0.001  |
| Pulmonary infection                          | 54(40.6)                                 | 0.007   | 22(68.8)                                    | 0.941   | 76(46.1)                    | 0.025   |
| Cardiovascular disease                       | 56(42.1)                                 | <0.001  | 3(9.4)                                      | 0.579   | 59(35.8)                    | <0.001  |
| Neurological diseases                        | 41(30.8)                                 | 0.347   | 22(68.8)                                    | 0.941   | 63(38.2)                    | 0.697   |
| Gastrointestinal pathology                  | 42(31.6)                                 | 0.238   | 2(6.3)                                      | 0.656   | 44(26.7)                    | 0.143   |
| Chronic/acute liver disease                 | 30(22.6)                                 | 0.352   | 9(28.1)                                     | 0.287   | 39(23.6)                    | 0.600   |
| Chronic/acute renal failure                 | 60(45.1)                                 | 0.027   | 6(18.8)                                     | -       | 66(40.0)                    | 0.001   |
| Haematological malignancy                   | 4(3.0)                                   | 0.120   | 2(6.3)                                      | 0.656   | 6(36.4)                     | 0.217   |
| Solid tumour                                | 12(9.0)                                  | 0.990   | 0(0)                                         | -       | 12(7.3)                     | 0.826   |
| Severe autoimmune diseases                  | 12(9.0)                                  | 0.990   | 0(0)                                         | -       | 12(7.3)                     | 0.826   |
| Congenital malformations/syndromes          | 0                                        | 0       | 15                                            | 0.365   | 5(3.0)                      | 0.799   |
| **Hematologic (nonmalignant)**              |                                          |         |                                              |         |                             |         |
| Diabetes mellitus                           | 45(33.8)                                 | 0.214   | 0(0)                                         | -       | 45(27.3)                    | 15.15   |
| HIV/AIDS                                    | 9(6.8)                                   | 0.419   | 0(0)                                         | -       | 9(5.5)                      | 0.503   |
| Severe trauma                               | 12(9.0)                                  | 0.990   | 2(6.3)                                      | 0.565   | 14(8.5)                     | 3(8.3)  |
| Risk factors (n, %)                          |                                          |         |                                              |         |                             |         |
| premature neonates ≤ 36 weeks*              | -                                        | -       | 28(87.5)                                     | 0.515   | 28(93.3)                    | 2(100.0)   |
| Very low birth weight neonates (<1500 g)*   | -                                        | -       | 19(59.4)                                     | 0.886   | 19(63.3)                    | 2(100.0)   |
| Presence of CVC                             | 57(42.9)                                 | 0.718   | 6(18.8)                                     | 0.546   | 63(38.2)                    | 14(38.9)   |
| Other invasive catheters                    | 51(38.3)                                 | 0.004   | 5(15.6)                                     | 0.460   | 56(33.9)                    | 4(11.1)   |
| Mechanical ventilation                      | 45(33.8)                                 | 0.002   | 19(59.4)                                     | 0.805   | 64(38.8)                    | 23(36.9)   |
| Receipt of corticosteroids                  | 27(20.3)                                 | 0.785   | 9(18.1)                                      | 0.287   | 36(21.8)                    | 6(16.7)   |
| Total parenteral nutrition                  | 57(42.9)                                 | 0.067   | 17(53.1)                                     | 0.512   | 74(44.8)                    | 21(58.3)   |
| Malnutrition                                | 36(27.1)                                 | 0.710   | 8(25.0)                                      | 0.752   | 44(26.7)                    | 11(30.6)   |
| Chemotherapy                                | 16(12.0)                                 | 0.324   | 2(6.3)                                       | 0.656   | 18(10.9)                    | 2(5.6)    |
| Abdominal surgery                           | 24(18.0)                                 | 0.676   | 0(0)                                         | -       | 24(14.5)                    | 7(19.4)   |
| Hemodialysis                                | 22(16.5)                                 | 0.303   | 0(0)                                         | -       | 22(13.3)                    | 8(22.2)   |
| ICU/PICU/NICU                               | 33(24.8)                                 | 0.094   | 32(100.0)                                    | 0.65    | 65(39.4)                    | 16(44.4)   |
| Neutropenia*                                | 13(9.8)                                  | 0.905   | 0(0)                                         | -       | 13(7.9)                      | 3(8.3)    |
| **Concomitant bacterial infections**        | 59(44.4)                                 | 0.047   | 27(84.4)                                     | 0.460   | 86(52.1)                    | 24(66.7)   |
| Septic shock                                | 8(6.0)                                   | <0.001  | 1(3.1)                                       | <0.001  | 9(5.5)                      | 30(66.7)   |

* Calculated as the percentage of the total number of patients.
Table 5. Factors associated with 30-days mortality by multivariate analysis*

| Variable                                | All patients                     | Adult patients                    |
|-----------------------------------------|----------------------------------|-----------------------------------|
|                                         | Odds ratio 95% confidence interval | P-value | Odds ratio 95% confidence interval | P-value |
| Median age                              | 1.02 0.973-1.065 0.444 1.03 0.957-1.109 | 0.427    | 0.04 0.002-0.695 0.028 0.04 0.001-1.233 | 0.066 |
| Length of hospital stay (days)           | 0.88 0.809-0.964 0.005 0.89 0.802-0.99 | 0.032    | 4.59 0.554-37.999 0.158 12.56 0.981-160.793 | 0.052 |
| Respiratory dysfunction                  | 13.78 2.254-84.198 0.005 22.57 2.014-252.84 | 0.011    | 2.50 0.464-13.425 0.287 1.19 0.191-7.392 | 0.854 |
| Pulmonary infection                      | 0.68 0.125-3.693 0.655 0.98 0.142-6.743 | 0.982    | 0.65 0.088-4.787 0.672 3.36 0.269-41.933 | 0.347 |
| Cardiovascular disease                   | 0.65 0.088-4.787 0.672 3.36 0.269-41.933 | 0.347    | 0.04 0.002-0.695 0.028 0.04 0.001-1.233 | 0.066 |
| Chronic/acute renal failure              | 2.50 0.464-13.425 0.287 1.19 0.191-7.392 | 0.854    | 0.04 0.002-0.695 0.028 0.04 0.001-1.233 | 0.066 |
| Her invasive catheters                   | 0.04 0.002-0.695 0.028 0.04 0.001-1.233 | 0.066    | 0.04 0.002-0.695 0.028 0.04 0.001-1.233 | 0.066 |
| Mechanical ventilation                   | 4.97 0.42-58.742 0.204             |         | 4.97 0.42-58.742 0.204             |         |
| Septic shock                            | 99.97 11.997-832.995 <0.001 89.72 10.161-792.184 | <0.001  | 99.97 11.997-832.995 <0.001 89.72 10.161-792.184 | <0.001 |
| Diabetes mellitus                       | 0.12 0.013-1.038 0.054             |         | 0.12 0.013-1.038 0.054             |         |
| C. albicans                            | 115(86.5) 29(87.9) 0.830 32(100.0) 3(100.0) - 147(89.1) 32(88.9) 0.972 |         | 115(86.5) 29(87.9) 0.830 32(100.0) 3(100.0) - 147(89.1) 32(88.9) 0.972 |         |
| Treatment with antifungal agents         | 71(53.4) 16(48.5) 0.614 24(75.0) 3(100.0) 0.324 95(57.6) 19(52.8) 0.599 |         | 71(53.4) 16(48.5) 0.614 24(75.0) 3(100.0) 0.324 95(57.6) 19(52.8) 0.599 |         |
| Species, n (%)                          | C. albicans 47(35.3) 18(54.5) 0.043 16(50.0) 0(0) 0.096 63 (38.2) 18 (50.0) 0.190 |         | C. albicans 47(35.3) 18(54.5) 0.043 16(50.0) 0(0) 0.096 63 (38.2) 18 (50.0) 0.190 |         |
|                                          | C. glabrata 46(34.6) 9(27.3) 0.424 15(46.9) 3(100.0) 0.078 61 (37.0) 12 (33.3) 0.681 |         | C. glabrata 46(34.6) 9(27.3) 0.424 15(46.9) 3(100.0) 0.078 61 (37.0) 12 (33.3) 0.681 |         |

ICU= intensive care unit; PICU= pediatric intensive care unit, NICU=neonatal intensive care unit

*Because the total number of pediatric patients (35 patients) and deaths (3 patients) were very small, multivariable logistic regression analysis was not performed in pediatric patients.
| Authors            | Country or region | Protective factor                                                                 | Predictors of 30-day mortality                                                                 | Reference |
|--------------------|-------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-----------|
| Ma et al           | China             | Presence of CVC                                                                   | -                                                                                               | 37        |
| Cortes et al       | Colombia          | Fluconazole therapy                                                               | -                                                                                               | 40        |
| Wang et al         | China             | antifungal therapy administered before microbiological documentation               | absence of antifungal therapies, receipt of mechanical ventilation and APACHE II score ≥20         | 41        |
| Tedeschi et al     | Italy             | central-venous-catheter removal and adequate and timely (within 72 h of drawing blood cultures) therapy | chronic-obstructive-pulmonary-disease and isolation of C. tropicalis                              | 42        |
| Li et al           | China             | proven catheter-related candidemia                                                | Severe sepsis or septic shock                                                                  | 35        |
| Gonzalez-Lara et al| Mexico            | Early CVC withdrawal and empirical antifungal therapy                             | severe sepsis and previous diagnosis of cirrhosis                                              | 43        |
| Jia et al          | China             | ICU admission, catheter-related candidemia, ascites, septic shock and concomitant bacterial infection | -                                                                                               | 18        |
| Ortega-Loubon et al| Spain             | prolonged mechanical ventilation, age and low lymphocyte count                   | -                                                                                               | 23        |
| Kato et al         | Japan             | follow-up blood culture, empiric treatment with fluconazole                        | age >65 years and SOFA score ≥6                                                                  | 5         |
| Ala-Houhala et al  | Finland           | Severity of underlying illnesses, ICU stay at the onset of candidemia and age >65 years | -                                                                                               | 4         |
| Medeiros et al     | Brazil            | older age, severe sepsis and hypotension                                          | -                                                                                               | 25        |
| Santolaya et al    | Chile             | mechanical ventilation and previous use of corticosteroids                        | -                                                                                               | 17        |
| Alkharashi et al   | Saudi Arabia      | use of broad-spectrum antibiotics and use of central venous catheters             | -                                                                                               | 24        |
| Xiao et al         | China             | GCS score, P/F ratio, MAP                                                           | -                                                                                               | 36        |

CVC: central venous catheter; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive care unit; SOFA: Sequential Organ Failure Assessment; GCS: Glasgow Coma Scale; P/F ratio: PaO2/FiO2 ratio; MAP: Mean arterial pressure.

**Figures**
Figure 1

Distribution of the fungal species according to different wards. FootNote: Others include C. guilliermondii (4), C. haemulonii (1) and C. inconspicua (1).