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ORIGINAL RESEARCH

Candidaemia: A 9-Year Retrospective Analysis of Epidemiology and Antimicrobial Susceptibility in Tertiary Care Hospitals in Western China

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Purpose: This investigation endeavors to scrutinize the resistance profiles to antifungal agents, alongside the clinical distribution of *Candida* isolates that yielded positive results in blood cultures at Suining Central Hospital spanning the years 2015 to 2023. The objective is to provide crucial epidemiological insights that may aid in early clinical intervention and judicious deployment of antifungal therapies.

Methods: This retrospective analysis analyses data on 182 different *Candida* strains with positive clinical blood cultures obtained from the Microbiology Laboratory of Suining Central Hospital over a period of nine consecutive years. The study involved identification of Candida species and assessment of resistance patterns to fungal drugs.

Results: Our analysis revealed that the median age of patients diagnosed with Candidaemia from the 182 strains was 62 years, with a distribution of 63.7% females and 36.3% males. Within the cohort of 182 Candida strains, *Candida albicans* constituted 32.4%, while *non-albicans Candida* species comprised 67.6% of the cases. Specifically, *Candida tropicalis* represented 37.4%, *Candida glabrata* 12.1%, *Candida parapsilosis* 11.0%,*Candida guilliermondii* 3.8%, and both *Candida krusei* and *Candida Dublin* accounted for 1.6% each. These Candida species were predominantly identified in intensive care units (ICU), hematology, gastroenterology, neurology centers, and endocrine metabolism units.

Conclusion: The findings of this investigation suggest a shift in the prevalence of non-*Candida albicans* species, notably *C. tropicalis*, as the predominant cause of Candidaemia at Suining Central Hospital, surpassing *C. albicans*. Although instances of antifungal resistance are infrequent, there has been a notable rise in resistance to azoles. This study provides important insights into the local epidemiology, which will be essential for informing the selection of empirical antifungal therapy and contributing to the global surveillance of antifungal resistance.

Keywords: candidemia, Candida species, antifungal agents, bloodstream

Introduction

Fungal infections play a substantial role in the mortality associated with infectious diseases worldwide. Candida bloodstream infections, commonly referred to as candidemia, are severe systemic infections that can result in disseminated fungal lesions in multiple organs. These infections are frequently linked to healthcare environments, particularly due to the increasing population of immunocompromised patients. Candida-induced bloodstream infections are characterized by a high mortality rate, which can reach up to 60% in critically ill patients.[1–3]

Hazrat Bilal et al analysed 18 studies in China mentioning mortality from all causes, where the median mortality rate associated with Corynebacterium diphtheriae was 27.3% with an interquartile range (IQR) of 13.60–38.30%.[4] However, another study in the relevant literature by Chinese scholars mentioned an overall mortality rate of 20.4%, 11.4% for paediatric patients and 22.3% for adult patients.[5] It is noteworthy that Candida-induced bloodstream infections,

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especially those associated with central venous catheters, have been increasing in incidence in recent decades. The multinational EPIC II study, which included more than 14,000 patients, highlighted Candida as the third most common cause of infection globally, and the second most common in North America and Western Europe.[3] The prevalence of Candida species across China exhibits regional disparities, with North China reporting the highest proportion of isolates at 23.07%. East China follows in frequency with 15.20%, then South China with 13.95%, Northeast China with 11.12%, Southwest China with 9.11%, Central China with 8.69%, and Northwest China with 8.20%. Notably, a significant 10.64% of the isolates originated from various locations, indicating a widespread distribution of Candida species throughout the country.[4] Significantly, mortality rates were notably higher in patients with Candida bloodstream infections compared to those with bloodstream infections caused by Gram-positive or Gram-negative bacteria. The 12-week mortality rate for candidaemia in North American studies ranged from 23.7% to 52.9%.[6] This underscores the severity and clinical impact of Candida-induced bloodstream infections, highlighting the importance of early detection and appropriate management strategies to improve patient outcomes.[3,7] Candida isolation and identification can still necessitate more than 48 hours, even with advancements in detection methods, the implementation of guidelines, and the availability of new effective treatments. Rapid and accurate identification of Candida species is crucial for timely initiation of appropriate antifungal therapy, underscoring the ongoing need for further improvements in diagnostic technologies to expedite the diagnosis and management of Candida infections.[8,9] Given the information provided, experts recommend that clinicians identify patients at risk of Candida infection by taking into account local epidemiology and relevant clinical indicators. Although resistance of Candida isolates to existing antifungal medications remains uncommon, there is a rising global trend of these microorganisms exhibiting resistance. This highlights the importance of vigilant surveillance, appropriate diagnostic strategies, and judicious use of antifungal agents to effectively manage Candida infections and address the potential challenges posed by emerging resistance patterns.[10,11] The compilation and analysis of epidemiological data regarding antifungal drug resistance are imperative for delineating the extent of the resistance phenomenon and for crafting strategic interventions aimed at promoting the prudent utilization of antimicrobial agents, thereby reducing the evolutionary impetus for resistance development.[12,13]

Materials and Methods

Data Collection

The aim of this retrospective investigation was to evaluate Candida isolates identified via blood cultures at Suining Central Hospital, China, spanning from January 1, 2015, to June 30, 2023. The study aims to understand the prevalence of Candida and antifungal drug susceptibility patterns, which are necessary for the control and treatment of candidiasis, Informing the development of empirical antifungal treatment strategies. The dataset, procured from the hospital's microbiological department, encompassed critical information such as the dates of blood cultures, clinical outcomes, Antifungal Susceptibility Testing (AST) profiles, demographic specifics (including age and gender), and the associated hospital wards. To avert any bias from repeated isolates, our examination was restricted to the initial pathogen detected in each individual case.

Pathogen Identification and Antimicrobial Susceptibility Test

Aerobic and anaerobic blood cultures were performed using the BACT/ALERT 3D system (bioMérieux, France), with incubation periods not exceeding five days. Positive cultures, as indicated by the instrument, were subjected to Gram staining. Subsequently, cultures exhibiting Candida growth were inoculated onto Columbia blood agar and Sabouraud dextrose agar (Kangtai, Wenzhou, China). Following a 48-hour incubation period at 37°C, the putative pathogens were identified through a combination of conventional biochemical assays and the Vitek-2 Compact system (bioMérieux, France). The in vitro susceptibility to antifungal agents, including fluconazole (FLC), voriconazole (VRC), itraconazole (ITC), 5-flucytosine (5-FC), and amphotericin B (AMB), was assessed using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution guidelines (M27-A3).[14] The minimum inhibitory concentration (MIC) for each Candida isolate was established after a 24-hour incubation period for a spectrum of antifungal agents. The MIC endpoints for 5-fluorocytosine (5-FC) and the azole antifungals were identified by a 50% reduction in fungal proliferation relative to the untreated control. For amphotericin B (AMB), the MIC endpoint was the lowest concentration that led to a complete suppression of visible fungal growth. Stringent quality control measures were implemented, with the inclusion of the reference strains *C. albicans* ATCC 90028 and *C. parapsilosis* ATCC 22019 in every assay to ensure reliability and reproducibility of results.

Statistical Analysis

The data were analyzed utilizing WHONET 5.6 software in accordance with the established version standards. A paired *t*-test was employed to discern any significant differences in the rates of positive blood cultures across categories of sex, age, and hospital wards. Comprehensive statistical analyses were conducted utilizing SPSS Statistics 28.0 software, developed by IBM Corporation, New York, USA.

Results

Species Distribution and Patient

Between January 1, 2015, and June 30, 2023, a cumulative total of 182 Candida strains were isolated from patients with positive blood cultures, corresponding to an overall incidence rate of about 0.2 cases per 1000 hospital admissions. *C. tropicalis* was the most prevalent, accounting for 37.4% of the isolates (68 out of 182), succeeded by *C. albicans* at 32.4% (59 out of 182), *C. glabrata* at 12.1% (22 out of 182), and *C. parapsilosis* at 11.0% (20 out of 182). A detailed annual breakdown of specific Candida strains isolated is depicted in Figure 1.

The median age among the 182 patients diagnosed with Candida bloodstream infections was 62 years, with ages ranging from 0 to 93 years. Our study revealed a notably elevated positivity rate of 60.4% (110 out of 182) among individuals aged 60 years and older. This pronounced disparity in positivity rates across different age groups underscores the increased vulnerability and potential for severe outcomes of Candida infections in the elderly population. Additionally, the current analysis demonstrated a higher prevalence of Candida bloodstream infections in females, with 116 cases representing 63.7% of the total, compared to 66 cases in males, which constituted 36.3% (p<0.01). Table 1 presents a comprehensive overview of the incidence rates and corresponding statistical significance (p-values) for Candida infections across various age groups and genders.

In this study, the top five departments identified for patient detection were the Intensive Care Medicine, Hematology, Gastroenterology Center, Neurology Center, and Endocrinology and Metabolism. The Department of Intensive Care Medicine exhibited a significantly higher detection rate compared to the other departments, with statistical significance denoted by P < 0.01. For a detailed illustration of these findings, please refer to Figure 2.

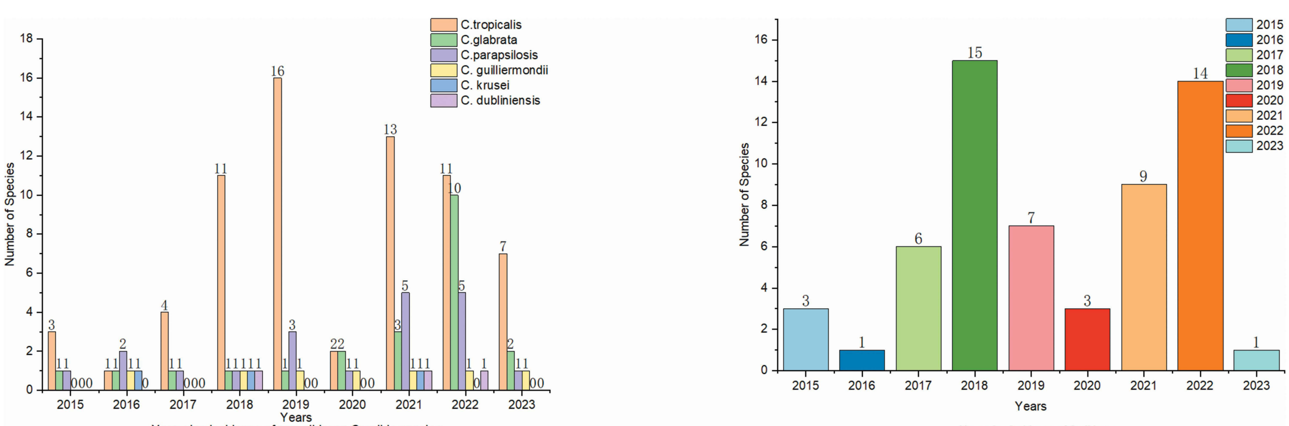

Figure 1 Candida species from Blood candidiasis reported in the past 9 years (2015–2023).

Table 1 Baseline Data of Patients

Year	Cases	M/F	Age Groups				p-Value[#]
			0–18	19–35	36–59	≥60	
2015	8	4:4	1	1	2	4	0.170
2016	7	3:4	0	1	2	4	0.043
2017	12	4:8	0	0	4	8	<0.01
2018	31	7:24	0	4	8	19	<0.01
2019	28	7:21	5	3	6	14	0.008
2020	9	3:6	0	2	0	7	0.001
2021	33	16:17	1	2	13	17	<0.01
2022	42	15:27	1	2	5	34	<0.01
2023	12	6:6	0	4	5	3	<0.01
SUM	182	66:116	8	19	45	110	<0.01
p-value	<0.01[#]	<0.01*					

Notes: M:F = Male ratio female.*Ratio paired *t*-test. # Student's *t*-test.

Antifungal Susceptibility Patterns of C. Albicans

Among *C. albicans* isolates, the commonly utilized azoles—fluconazole, voriconazole, and itraconazole—consistently demonstrated a sensitivity rate exceeding 75%. In the realm of other antifungal agents, a mere single strain exhibited resistance to amphotericin B during the year 2018, while sensitivity to 5-Flucytosine was uniformly high at a 100% rate across all strains. The year-wise assessment of antifungal susceptibility for *C. albicans* to the full spectrum of tested antifungal agents is delineated in Figure 3.

Antifungal Susceptibility Patterns of Non-Candida Albicans Species

Among the 68 *C. tropicalis* strains examined in this study, resistance to the azoles fluconazole, itraconazole, and voriconazole was observed at a rate of 5.9%. Each of these isolates remained fully susceptible to both amphotericin

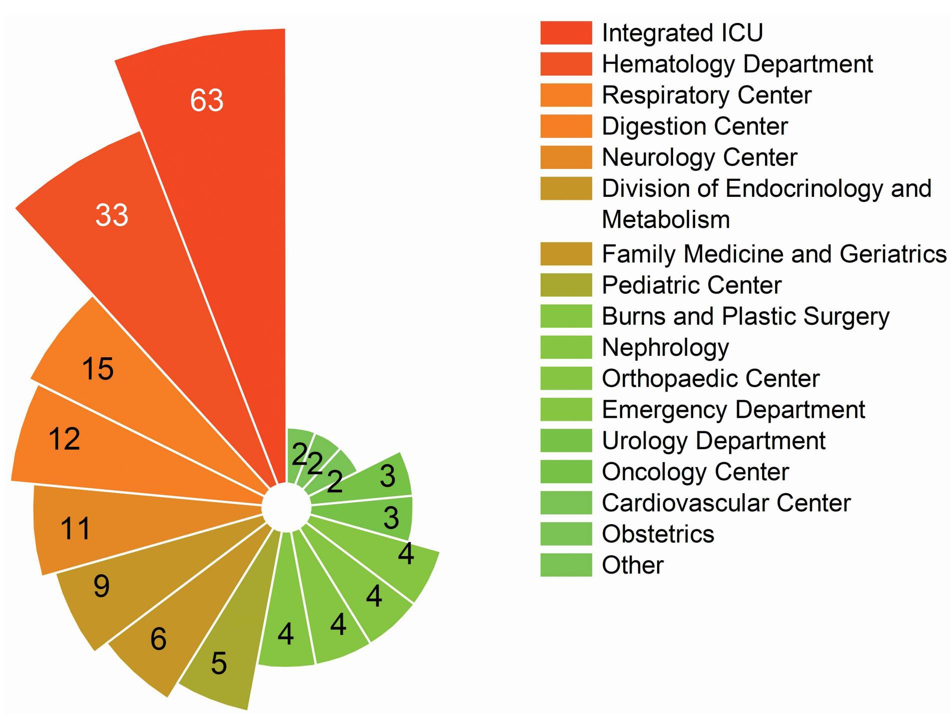

Figure 2 Distribution of clinical departments with positive blood cultures for Candida, 2015–2023.

Figure 3 Year-wise antifungal susceptibility patterns of *C. albicans* against all tested.

B and 5-fluorocytosine. Among the 22 smooth *C. glabrata*, resistance to the same azoles was noted at rates of 13.6% for fluconazole and itraconazole, and 18.2% for voriconazole. Furthermore, within the 20 *C. parapsilosis*, resistance to these azoles was identified at rates of 20.0% for fluconazole, 5.0% for itraconazole, and 10.0% for voriconazole. Notably, in 2021, a single strain was found to be resistant to amphotericin B. Figure 4 encapsulates the antifungal susceptibility profile of non-Candida albicans species.

Discussion

Enhanced comprehension of the local epidemiological patterns and the prevalence of antifungal resistance is imperative for clinicians to devise evidence-based therapeutic strategies for antifungal prophylaxis in their patients, particularly during the interim period prior to the availability of culture-based drug susceptibility results.[15] To achieve this objective, we undertook a nine-year retrospective surveillance study, laboratory-based, focusing on Candidaemia within our geographical region.

Our data showed that the incidence of Candida infections was 0.2 per 1000 hospital admissions, which is similar to the nationally reported average annual incidence of 0.26 per 1000 admissions for candidaemia, and is also consistent with the range of incidence reported in the United States, which is between 0.28 and 0.96 per 1000 hospital admissions.[5,16–19] In comparison, the incidence of Candida infections in Europe is reported to be within a slightly lower range, specifically from 0.20 to 0.38 cases per 1000 admissions,[20] In contrast to the United States and Europe, Norway exhibits a lower incidence rate of Candida infections, with only 0.17 cases per 1000 admissions reported,[21] Data from Hungary reflect a slightly higher range of Candida infections compared to Norway, with an incidence rate between 0.20 to 0.40 cases per 1000 admissions,[22] In Switzerland, the reported incidence of Candida infections is relatively stable, with a rate of 0.27 cases per 1000 admissions[23] Studies akin to this one consistently report incidence rates of Candida infections that are similar to, and in some cases lower

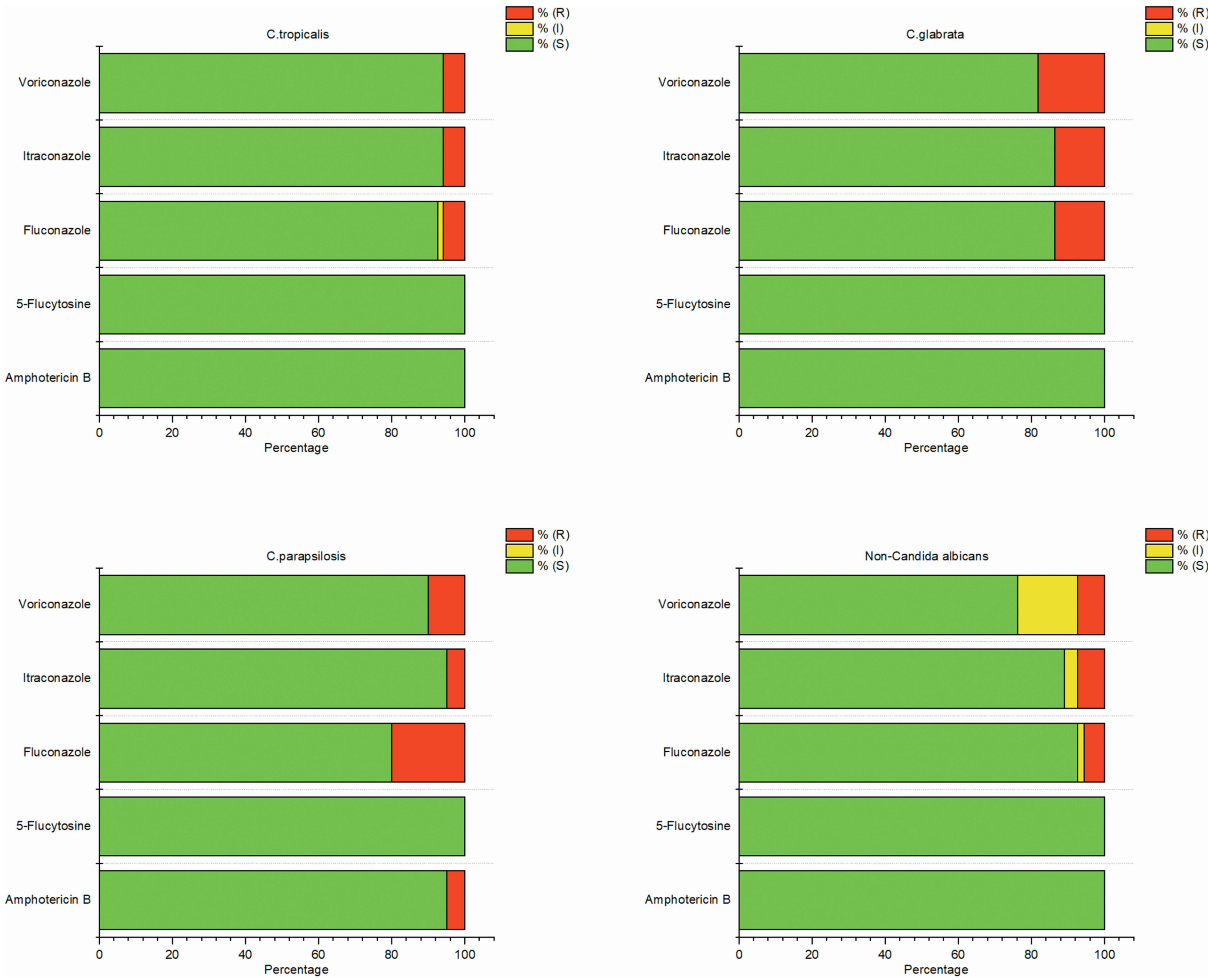

Figure 4 Antifungal drug sensitivity patterns of non-albicans *C. albicans* to all drugs tested.

than, those observed in Italy, where the rate is recorded at 0.38 per 1000 admissions,[24] In contrast to several other European nations, Spain exhibits a higher incidence of Candida infections, with rates ranging from 0.76 to 0.81 cases per 1000 admissions,[25] In Canada, the incidence rate of Candida infections is noted to be 0.45 cases per 1000 admissions, aligning with moderate infection rates observed in certain European countries.[26]

The median age of patients with cases in our dataset was 62 years, which is similar to the median age of 65 years reported in this country but exceeds the median age reported in corresponding studies in the United States, Brazil, and elsewhere.[5,27,28] This observation is indicative of a significant proportion of elderly individuals within our dataset. Additionally, a substantial majority of the patients were admitted to the Intensive Care Unit (ICU), constituting 35% of the total cases, which aligns closely with the 38% figure reported in studies from Brazil.[27] The significance of surgical interventions and the positioning of the Intensive Care Unit (ICU) within the hospital layout is highlighted as pivotal factors in the epidemiology of candidiasis.

Over the past decade, *C. albicans* has remained the predominant species associated with candidiasis. However, there has been a notable global rise in the incidence of candidiasis attributed to other Candida species, including *C. tropicalis, C. parapsilosis, C. glabrata*, and *C. krusei*. Concurrently, there has been a marked increase in the diagnosis of candidaemia caused by *non-Candida albicans* species.[29,30] While the precise etiology underlying the rise of *non-albicans Candida* species remains elusive, several medical conditions are believed to contribute to the increased risk of candidiasis caused by these yeasts. Notably, candidaemia characterized by pseudohyphae has been linked to the use of vascular catheters and the administration of parenteral nutrition.[31,32] Our surveillance data are in agreement with available reports showing that Candida albicans accounted for only 32.4% (59 out of 182) of the Candidaemia isolates. In contrast, Candida tropicalis was the predominant non-albicans Candida associated with haemorrhagic manifestations. These findings are consistent with a study conducted in Pakistan. However, data from two other studies in the country showed that the most common species remained Candida albicans in 40.3% of cases.[5,33] Recent studies have indicated a shift in the prevalence of Candida species, with Candida tropicalis emerging as a more prominent haemorrhagic pathogen than Candida albicans. Consistent reports from geographically diverse regions, including Singapore, Taiwan, and Brazil, have highlighted that Candida tropicalis is now the most prevalent species among non-Candida albicans isolates. However, it is noteworthy that two studies conducted in China have demonstrated a different trend, showing that Candida albicans remains the most commonly identified species. This shift in epidemiological patterns underscores the need for a nuanced understanding of Candida species beyond the traditional focus on *C. albicans*.[4,5,34–36] This is similar to data from other parts of the globe, such as the United States, Europe and South America, where Candida albicans remains the predominant strain associated with candidiasis.[27,37,38] The escalating prevalence of *non-Candida albicans* species could be attributed, in part, to the heightened utilization of fluconazole in both therapeutic and prophylactic settings.[39]

Among the seven Candida species implicated in Candida bacteraemia within our current dataset, *C. auris* and *C. dubliniensis* were the least frequently isolated, each representing 1.6% of the total isolates. Similar to the low detection rate of 2.25% reported in other studies in China.[4] Notably, *C. auris* is recognized as a significant pathogen among patients suffering from haematological malignancies and is also frequently encountered in individuals on extended azole prophylaxis.[15,40]

C. tropicalis, along with *C. parapsilosis* and *C. glabrata*, constituted 89.4% of the *non-Candida albicans* isolates. The considerable variability observed in the distribution of these species implies that factors beyond azole utilization significantly contribute to their prevalence, with demographic traits and the use of antibiotics being key considerations.[34,41]

Our findings revealed a significant predominance of Candida tropicalis, representing 37.4% of all identified Candida isolates. Furthermore, pseudohermaphroditic Candida species, inclusive of Candida tropicalis, are found to constitute a variable proportion of Candida infections across different regions. In Europe, these species account for 2 to 10% of cases, while in the United States and Canada, the prevalence is somewhat higher, ranging from 10 to 12%.[20,23,28,41–49] It is of interest to highlight that three distinct studies, each from China, Brazil, and Saudi Arabia, have reported a modestly lower prevalence of Candida tropicalis. These studies indicate that 21.8%, 21%, and 20.7% of Candida infections in their respective regions are attributable to this particular species.[4,27,50] We did not discern any specific distinguishing characteristics between the research centers that reported lower versus higher proportions of Candida species.

Staphylococcus parapsilosis was found in 11.0% of Candida cases in our dataset, which is similar to the 11.37% reported in other studies in China.[4] The prevalence of this species as a causative agent of candidiasis exhibits significant variability across global studies, with ranges reported from 7.0% to 21% in the United States, 6.9% to 30.0% in Europe, and notably higher at 25.0% in Brazil.[20,27,41,51] While the precise causes of the observed wide variations remain elusive, they could potentially be associated with the proportion of neonates included in each study.

In our investigation, we observed that Candida albicans exhibited resistance to fluconazole and voriconazole at rates of 15.3% and 13.6%, respectively. These figures stand in contrast to the 9.34% and 38.79% resistance rates reported in a study from Guangdong. The Smooth Candida complex demonstrated a resistance rate of 13.6%, a finding that diverges from the Guangdong study's indication of full sensitivity to azole drugs.[52] Furthermore, the resistance rates for the Near Smooth Candida complex were recorded at 20.0% and 10.0%, respectively, which are markedly higher than the rates documented in a Beijing-based study. Conversely, Candida tropicalis presented a fluconazole resistance rate of 5.9%, a statistic that is notably lower than the 17.2% resistance rate reported in the Beijing study.[6]

This observed variability in resistance patterns may be ascribed to the distinct characteristics of patient cohorts and regional differences in antifungal stewardship practices.[53,54] The potential link between elevated levels of resistance and the extensive application of fluconazole for both prophylactic and therapeutic purposes is a topic of considerable debate within the clinical community, with opinions remaining divided and the issue still considered contentious.[55] The current guidelines from the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) advocate for the employment of echinocandin antifungals as the preferred first-line empirical therapy, to be administered before conducting definitive species identification and antifungal susceptibility testing.[56]

It should be highlighted that our evaluation and discourse are confined to cases within our hospital's purview, given a modest overall sample size. This could potentially be swayed by various factors, including the patient count, the tier of medical care provided, and the spectrum of patient profiles present.

Conclusions

This research offers crucial new insights into the prevalence of haematological candidiasis, detailing species distribution and the susceptibility of Candida to a range of antifungal medications. Notably, our findings indicate a higher detection rate of Candida tropicalis compared to Candida albicans. In scenarios where antifungal drug susceptibility testing outcomes are not available, Amphotericin B and 5-fluorocytosine are recommended as the drugs of first choice.

Data Sharing Statement

All pertinent data utilized in the analysis and the subsequent generation of findings presented within this study are fully encompassed within the content of this manuscript.

Ethics Approval and Consent to Participate

This study received approval from the Ethics Committee of Suining Central Hospital, with the assigned approval number KYLLKS20230147, and it specifically waived the necessity for obtaining written informed consent from individual patients. The strains analyzed were derived from routine laboratory diagnostics and did not involve the use of any human genetic material. The research was conducted strictly following the ethical principles laid down in the Declaration of Helsinki.

Consent for Publication

All authors have thoroughly reviewed the manuscript and have provided their explicit consent for publication.

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Author Contributions

Each author has made substantial and meaningful contributions to this research, which encompass the original concept, study design, execution, data acquisition, analysis, and interpretation of findings. All authors were actively involved in drafting the manuscript, revising it critically for important intellectual content, and have provided their final approval of the version submitted for publication. Additionally, a consensus has been reached on the choice of journal to which the manuscript has been submitted. The authors collectively agree to be responsible for the integrity of all aspects of the work.

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Disclosure

The authors hereby certify that there are no conflicts of interest, financial or otherwise, associated with this research work.

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