Species distribution, antifungal susceptibility pattern and associated factors of *Candida* blood stream infections in Sri Lanka from 2018 to 2022

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(Keywords: Candidemia, *Candida* species)

Abstract

Introduction: Candidemia can be life-threatening in immunocompromised individuals thus, prompt diagnosis and treatment with antifungal agents is mandatory for successful outcome.

Surveillance data on species distribution, antifungal susceptibility and associated factors of candidemia is utmost important to decide on empiric antifungal therapy, to impose infection control measures as well to promote antifungal stewardship in a country.

Therefore, this study was aimed at retrospective review of data on candidemia at Mycology Reference Laboratory in Sri Lanka for 5 years duration to identify the species causing candidemia, their antifungal susceptibility pattern and associated factors.

Results: A twofold rise in candidemia cases were seen during this 5-year duration compared to previous 7 years (2011-2017). Predominant species causing candidemia was *C. tropicalis* (35%) followed by *C. parapsilosis* (33%). *C. albicans* was the 3rd commonest species causing candidemia in Sri Lanka.

There were 3% *C. glabrata* cases, 2% *C. guilliermondii* and 1% *C. famata* and *C. krusei* cases. Importantly two sequencing confirmed *C. auris* cases were identified for the first time in Sri Lanka in 2021.

Overall good antifungal susceptibility was seen for both fluconazole and amphotericin B and there were only 7% and 1.6% resistance respectively.

Long term hospital stay (47%) was commonly seen in this study group followed by use of broad-spectrum antibiotics (24%) and involvement of gastro-intestinal tract (21%).

Conclusion: Candida tropicalis is the commonest species causing candidemia in Sri Lanka. Common *Candida* species had good susceptibility to antifungals. Long term hospital stay was associated with candidemia in majority of patients.

Introduction

Candida sp. can cause a diverse spectrum of disease ranging from superficial candidiasis to invasive disease (1). Among different manifestations of candidiasis, candidemia is an alarming condition due to its high mortality rate (47%). Mortality is even higher in patients with septic shock following candidemia (1,2).

Species distribution of candidemia has been changed over past years. There is a global shift towards nonalbicans *Candida* species where *Candida albicans* the previously dominating pathogen accounts only for about 50% of the isolates according to many surveys. *C. glabrata* has emerged as an important pathogen in United States, Canada and in Northern Europe where *C. parapsilosis* is more significant in Asia, South America and in South Europe. The direction towards nonalbicans *Candida* is a threatening condition due to their resistant nature to commonly used antifungals. Furthermore, the species identification is important as they differ in virulence as well. *C. krusei* and *C. parapsilosis* are known to be less virulent than *C. albicans*, *C. glabrata* and *C. tropicalis* (3).

The Global Antimicrobial Resistance Surveillance System (GLASS) supports the implementation of the Global Action Plan on Antimicrobial Resistance by strengthening surveillance on antimicrobial resistance worldwide. As an initial approach a protocol was given by WHO 2019 to include *Candida* spp. into GLASS and at the early-stage *Candida* isolates causing blood stream infections will be included in this surveillance with antifungal susceptibility pattern to assess the emerging resistance in *Candida* spp. worldwide (4).

Though, there is a growing concern on fungal diseases globally due to increased immunocompromised

Ceylon Medical Journal 2024; **69:** si 47-53

DOI: http://doi.org/10.4038/cmj.v69iSI3.9968

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population, quality data is lacking in the disease distribution and antifungal resistant patterns. Therefore, in 2022 WHO developed the 1st fungal priority pathogens list (WHO FPPL) to strengthen the global response towards this aspect aiming at more researches and policy interventions and they have included *C. albicans* and *C. auris* in the critical category (5).

But unfortunately, there is a scarcity of candidemia surveillance data in Sri Lanka due to many constraints.

Therefore, this study was aimed at evaluation of species causing candidemia from the year 2018 to 2022 using the data available at National Mycology Reference Laboratory in Sri Lanka. In addition, special attention was given to the antifungal susceptibility pattern of *Candida* species during this analysis.

Furthermore, demographic data and risk factors of candidemia patients were assessed using the available data at Mycology Reference Laboratory in Sri Lanka.

Objectives

Objectives of this study was to assess the species distribution, antifungal susceptibility pattern and associated factors of *Candida* blood stream infections in Sri Lanka from 2018 to 2022.

Methodology

A retrospective review of mycology documents containing candidemia isolates in the Department of Mycology at Medical Research Institute, Colombo was performed during 3 months duration (21.06.2023-20.09.2023).

Candidemia patients treated at different hospitals in Sri Lanka whose *Candida* species were further identified at Department of Mycology at MRI from January 2018 to December 2022 was included in the study.

Results

Altogether 2800 *Candida* isolates were further identified at Mycology Reference Laboratory during the study period, but only 2692 were from peripheral blood cultures and the rest (n=108) were central line related cultures. Since this study was aimed at candidemia blood stream infections only peripheral blood culture isolates were included in the data analysis.

One thousand fifty-six blood samples for fungal culture were received to Mycology Reference Laboratory, MRI during 2018 to 2022 and only 19 samples have become positive for *Candida* species (1.8%). The sample size 2692 of this study includes all the candidemia isolates sent to Mycology Reference Laboratory as well as the 19 positive blood culture isolates at the Mycology Reference Laboratory.

This study included candidemia isolates from all the provinces in Sri Lanka and majority were from Western Province (n=1723/2692, 64%) followed by Southern Province (n=395,14.67%).

Highest number of candidemia isolates were received from National Hospital of Sri Lanka (NHSL) in Western Province and it was 28.86% (n=777/2692). Second highest number was received from Karapitiya Teaching Hospital in Southern Province (13.48%, n=363/2692). Apart from that 8.80% (n=237/2692) samples were received from National Cancer Institute, 6.65% (n=179/2692) were from Colombo South Teaching Hospital and 6.39% (n=172/2692) were from largest children's hospital (Lady Ridgeway Hospital) of Sri Lanka.

Majority of patients with candidemia were adults aged more than 41 years (60.44%, n=1514/2505) and there was a male predominance (56.62%, n=1304/2303). Nearly 8% of the isolates were from neonates (n=189/2505) and 6-12-year-old age category had the lowest number of candidemia cases (2.79%, n=70/2505). Age was not mentioned regarding 187 candidemia isolates.

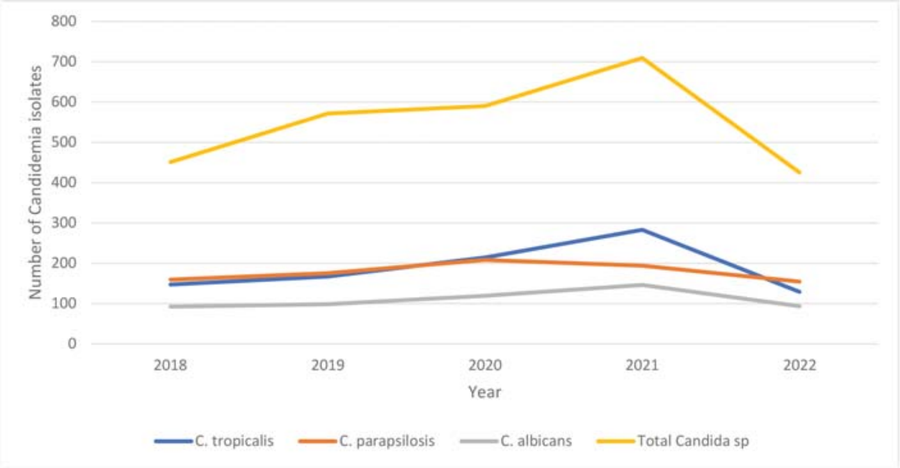


Figure 1. **Distribution of total number of *Candida* sp. and three common *Candida* species over 5 years.**

Figure 1 elaborates the total number of *Candida* isolates further identified at MRI (n=2692). It includes positive *Candida* blood cultures at MRI (n=19) and positive *Candida* blood culture isolates sent from other hospitals (n=2673).

There had been an increase in number on candidemia isolates received to MRI from 2018 to 2021 and a sudden drop in 2022 as illustrated in the above graph. This surge of candidemia cases in 2019 to 2021 could be a reflection of COVID-19 pandemic associated infections.

Overlapping results were observed between the numbers of *C. tropicalis* and *C. parapsilosis* during 5 years but *C. albicans* had remained lower than *C. tropicalis* and *C. parapsilosis* throughout the time.

Out of positive peripheral blood cultures only 20.3% isolates were *Candida albicans* (n=548/2692) and 79.7% were non-Candida *albicans* species (n=2,147/2692). *Candida* tropicalis dominated non-Candida *albicans* group accounting 34.9% of all candida isolates (n=940/ 2692) followed by *Candida parapsilosis* (33%, n=890/ 2692).

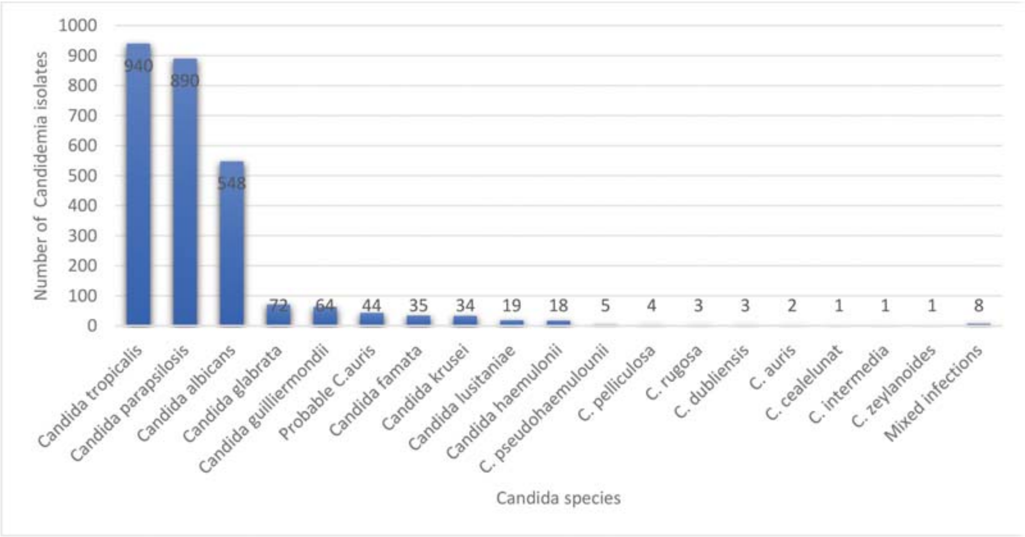


Figure 2. **Species distribution of different *Candida* species during 2018 to 2022.**

In addition, there were 2.7% (n=72/2692) *Candida glabrata*, 2.4% (n=64/2692) *Candida guilliermondii*, 1.3% (n=35/2692) *Candida famata* and 1.3% (n=34/2692) *Candida krusei*.

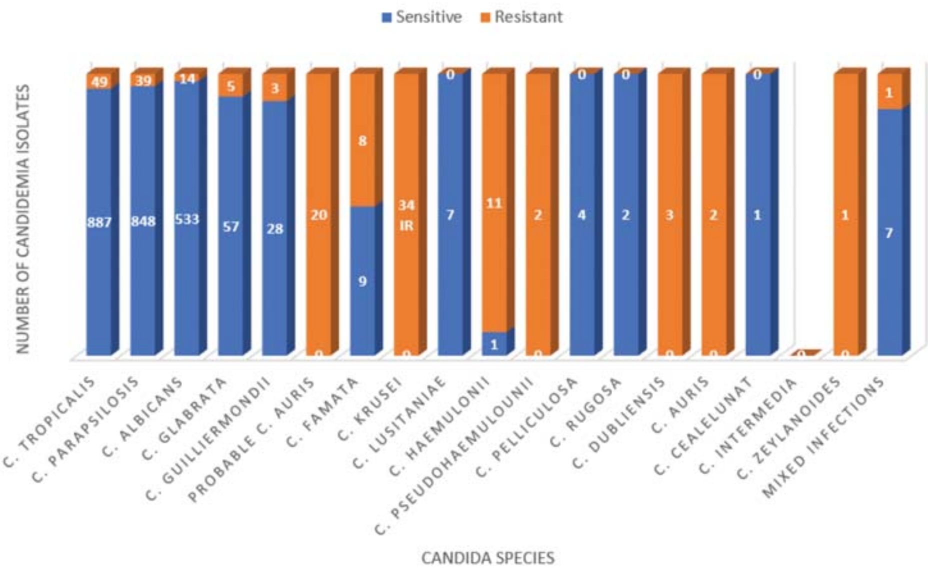
There were fewer number of other *Candida* species such as 0.7% (n=18/2692) *Candida haemulonii*, 0.7% (n=19/2692) *Candida lucitaniae* and 0.2% (n=5/2692) *Candida pseudohaemulonii*.

Importantly there were 2 sequencing confirmed *Candida auris* blood stream infections and another 44 isolates (1.6%) were identified as probable *C. auris* with available facilities.

There were 4 cases of candidemia mixed infections (two cases of *C. albicans* and C. krusei, one case of *C. tropicalis* and *C. krusei* and another case of *C. tropicalis* and *C. parapsilosis*) and 4 other cases of mixed infections due to *Candida* and non-candida species (two cases of *C. parapsilosis* and *Trichosporon* sp., one case of *C. guilliermondii* and *Geotrichum* sp. and another case of *C. tropicalis* and *Trichosporon* sp.).

Antifungal susceptibility test (AFST) was performed for majority of the isolates using disc diffusion method or E strip method and interpreted according to CLSI guideline. Amphotericin B MIC values by E strip method were interpreted according to the Epidemiological Cut-Off (ECV) values given by CLSI and amphotericin B disc diffusion tests were interpreted according to quality control limits given by the manufacture.

Fluconazole AFST was performed in 2576 *Candida* isolates (95.69%) and majority were sensitive to fluconazole (n= 2384,92.55%). Altogether, 192 (7.45%) *Candida* isolates were resistant to fluconazole. Fluconazole resistance rate was higher in non-*Candida albicans* group compared to *C. albicans*.



IR – Intrinsically Resistant

Figure 3. **Fluconazole susceptibility pattern of candidemia isolates.**

Only 2.56% (n=14/547) *Candida albicans* were resistant to fluconazole while 5.24% (n=49/936) of *Candida tropicalis* had resistant zones to the same. Thirty-nine isolates (4.40%) of *C. parapsilosis*, five isolates of (8.07%) *C. glabrata* and two confirmed *C. auris* isolates were also resistant to fluconazole. Out of probable *C. auris* isolates AFST for fluconazole was tested only for 20 and all of them showed resistance and majority of *C. haemulounii* were also resistant fluconazole.

Out of 8 mixed infections only one *C. parapsilosis* was resistant to fluconazole.

Amphotericin B AFST was performed in 73.29% (n=1973/2692) of isolates and majority were within sensitive range. All together 1.57% (n=31/1973) of Candida isolates were resistant to amphotericin B. Two confirmed *C. auris* isolates and majority of probable *C. auris* isolates (86.67%, n=13) were resistant to amphotericin B.

All the tested *C. tropicalis* (n=739) were sensitive to amphotericin B. *C. albicans* and *C. parapsilosis* also had more than 99% sensitivity (only one isolate each was resistant) to amphotericin B, whereas *C. krusei* and *C. glabrata* showed relatively lesser sensitivity (96.43%, n=27/28 and 94.23%, n=49/52 sensitivity respectively).

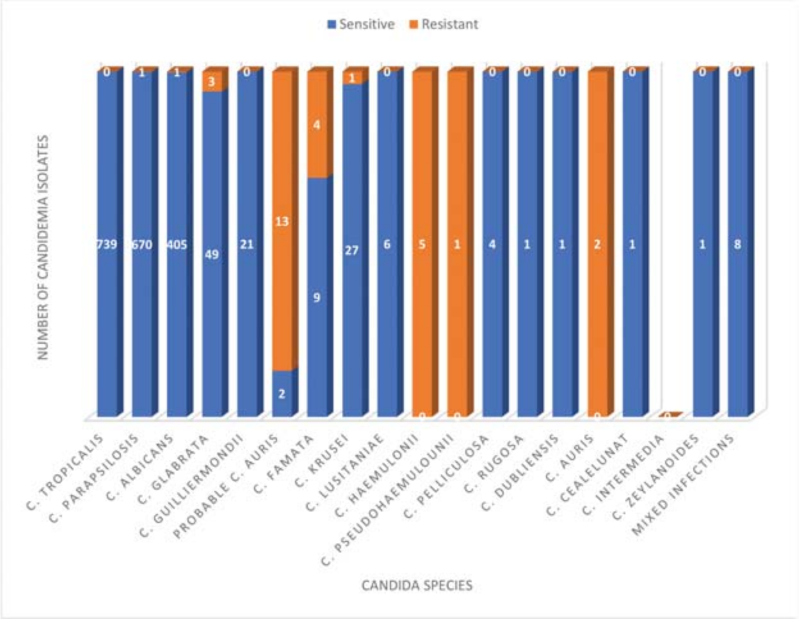


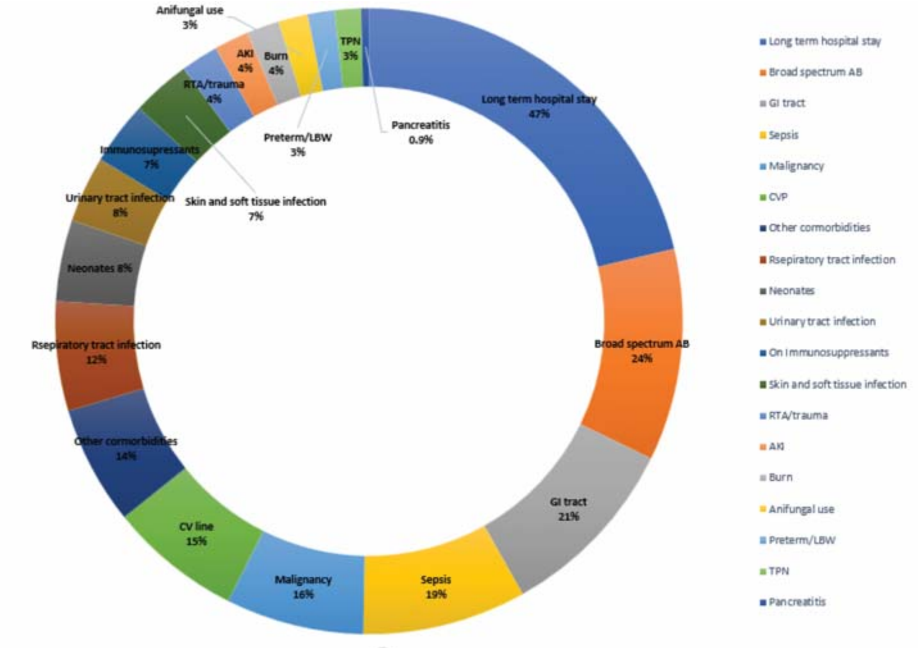
Figure 4. **Amphotericin B susceptibility pattern of candidemia isolates.**

Amphotericin B AFST was performed only for 21 *C. guilliermondii* isolates and all showed lower MIC values (≤1 µg/ml).

Out of the 13 *C. famata* isolates only 9 had lower MIC values (≤1 µg/ml) for amphotericin B (69.23%) and all 5 tested *C. haemulonii* had higher MIC values for amphotericin B (≥1 µg/ml)

AFST for echinocandins were performed only for 6 isolates due to unavailability of the drug in Sri Lanka. One *C. famata* showed higher MIC to fluconazole (>256 µg/ml) and anidulafungin (>32µg/ml) whereas it had lower MIC to amphotericin B (0.75 µg/ml) and caspofungin (0.012µg/ml). Other 5 isolates had lower MIC values for echinocandins (2 probable *C. auris*, 2 *C. tropicalis* and 1 *C. parapsilosis*).

Associated factors for candidemia were mentioned in only 75.97% (n=2045/2692) cases. Long term hospital stay was seen in majority of cases (46.80%, n=957/2045) followed by use of broad-spectrum antibiotics which was seen in 24.06% of cases (n=492/2045).



AKI – Acute kidney injury, LBW – low birth weight, TPN – Total Parenteral Nutrition,
GI – Gastrointestinal, CV line – Central venous line

Figure 5. **Percentage distribution of associated factors of candidemia cases.**

Involvement of gastrointestinal tract (trauma, surgery etc.) was observed in 433 cases (21.17%) of the study group. 18.57% (n=379) of patients were in sepsis/severe sepsis at the time of candidemia. In addition, malignancy (solid organ or hematological) was associated in 320 (15.65%) of the patients and 307 (15.01%) patients had Central Venous Catheter at the time of blood culture positivity.

There were 62 (3.03%) preterm and low birth weight babies and 147 patients (7.19%) who were on immunosuppressants with candidemia. Seventy-six patients (3.72%) had developed candidemia following burn injury and 61 patients (2.98%) had been on total parenteral nutrition (TPN).

Sixty-eight patients (3.33%) had recent exposure to antifungals 18 patients (0.88%) had pancreatitis.

Discussion

Candida sp. is a commensal of human body which can be pathogenic in susceptible hosts. Though more than 200 species of *Candida* have been identified so far only about 10% are recognized to cause infections in humans. Over past two decades it has emerged as one of the most important organisms causing nosocomial blood stream infections in both children and adults worldwide (6).

Speciation of *Candida* causing invasive infections is important since antifungal susceptibility differs according to the species (5). According our study, majority of candidemia cases were caused by non-*Candida albicans* species and only 1/5th (20.3%) of cases were caused by *Candida albicans*. *Candida tropicalis* ranked 1st out of all *Candida* species (34.9%) and *C. parapsilosis* also has contributed to a greater extent (33%). Therefore, almost 88% of candidemia cases in Sri Lanka is caused by 3 main *Candida* species namely *C. tropicalis, C. parapsilosis* and *C. albicans* and it rises up to 92% when *C. glabrata* (2.7%) and *C. krusei* (1.3%) are also included. Other *Candida* species were less commonly encountered.

Data from a Global Antifungal Surveillance Study across 39 countries has revealed that 92% of cases of candidemia are caused by only five common species of *Candida (C. albicans, C. glabrata, C. tropicalis, C. parapsilosis* and *C. krusei*) and it was almost similar to our data. But *Candida albicans* has been identified as the frequently isolated species of candidemia worldwide resulting 62% of cases whereas it is the 3rd commonest species in our setting (7).

The species distribution of candidemia cases is almost similar to the previous data (2001 to 2017) of Department of Mycology, MRI. But the proportion of *C. tropicalis* has come down from 53.2% to 34.9% whereas significant increase is seen among *C. parapsilosis* (from 19.8% to 33%) and *C. albicans* (14.7% to 20.3%). Interestingly there had been a decrease in cases of *C. glabrata* (from 8.7% to 2.7%) and no significant difference was observed among other species such as *C. guilliermondii*, *C. famata*, *C. krusei* and *C. lucitaniae* (8).

Importantly, with the improvement of diagnostic facilities two cases of *C. auris* blood stream infections (confirmed by sequencing) were detected during past 5 years and 44 other isolates were identified as probable *C. auris* cases (pending molecular diagnosis).

In addition, *C. guilliermondii* (2.4%), and probable *C. auris* (1.6%) cases have exceeded the number of *C. krusei* (1.3%) in this study.

On the other hand, the total number of candidemia isolates has been doubled during this 5-year duration when compared to the past 7 years. 2011 to 2017 only 1344 candidemia isolates were received to MRI for further identification but there were 2692 isolates during 2018 to 2022. Increased awareness of fungal infections, improved diagnostic facilities and growing number of immuno-compromised patients must have resulted in this surge of candidemia in Sri Lanka (8).

Overall fluconazole resistance was 7% and amphotericin B resistance was 1.6% in this population. All common *Candida* sp. had >90% sensitivity to fluconazole except for *C. krusei* which is intrinsically resistant. Out of that *C. albicans* showed the highest sensitivity (97%) and *C. glabrata* and *C. guilliermondii* showed comparatively lower susceptibility (92% and 90% respectively). But all tested *C. auris*, probable *C. auris*, >90% *C. haemulonii* and nearly half of *C. famata* were resistant to fluconazole emphasizing the importance of species identification of candidemia isolates. Similarly, common *Candida* species had good sensitivity to amphotericin B while all tested *C. auris*, *C. haemulonii*, >80% probable *C. auris* and 30% *C. famata* had higher MIC values challenging the management of such patients in resource limited setting such as Sri Lanka.

Immunocompromised states such as malignancies, glucocorticoid use and other conditions like use of central venous catheters, broad spectrum antibiotics, total parenteral nutrition, being a preterm infant, critically ill patients and abdominal surgery are some of the risk factors identified for candidemia (9).

According to this study long term hospital stay was found to be the commonest cause associated with candidemia which was seen nearly half of the patients. About 1/4th of patients was on broad spectrum antibiotics and 1/5th had gastro-intestinal tract involvement making them more susceptible for candidemia infections. Sepsis, malignancies and presence of central venous lines also have contributed to candidemia in a considerable proportion while other factors accounted <10%. Majority of patients had more than one factor associated with candidemia in this study group.

Conclusion

C. tropicalis is the commonest species causing candidemia in Sri Lanka followed by *C. parapsilosis* and *C. albicans*. Multidrug resistant *C. auris* is an emerging species which needs special caution.

Fluconazole resistance rate was higher in non-*Candida albicans* group. Nearly half of the patients with candidemia had long term hospital stay in this population.

Acknowledgements

We are grateful to the staff of Department of Mycology, Medical Research Institute, Colombo, 08, Sri Lanka.

Author contributions

PGRUM involved in data extraction from records, data entry, analysis and manuscript writing. PIJ supervised this research project providing guidance in planning, carrying out the research methodology, interpretation of results and presentation of the work.

Conflicts of interest

None.

Ethical approval

Ethical clearance was obtained from Ethics Review Committee of the Medical Research Institute, Sri Lanka (Project number - 02/2023).

Sources of funding

None.

Abbreviations

AFST – Antifungal susceptibility test

MRI – Medical Research Institute

MIC – Minimum Inhibitory Concentration

References

1. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, *et al*. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 201; **62**(4): e1-50.
2. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic Shock Attributed to Candida Infection: Importance of Empiric Therapy and Source Control. *Clinical Infectious Diseases* 2012; **54**(12): 1739-46.
3. Kullberg BJ, Arendrup MC. Invasive Candidiasis. Campion EW, editor. *N Engl J Med*. 2015; **373**(15): 1445-56.
4. Global Antimicrobial Resistance Surveillance System (GLASS) early implementation protocol for the inclusion of Candida spp. Geneva: World Health Organization; 2019 (WHO/WSI/AMR/2019.4 Eng). Licence: CC BY-NC-SA 3.0 IGO.
5. WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
6. Alkharashi N, Aljohani S, Layqah L, Masuadi E, Baharoon W, AL-Jahdali H, *et al*. *Candida* Bloodstream Infection: Changing Pattern of Occurrence and Antifungal Susceptibility over 10 Years in a Tertiary Care Saudi Hospital. *Canadian Journal of Infectious Diseases and Medical Microbiology*. 2019; **2019**: 1-9.
7. Guinea J. Global trends in the distribution of Candida species causing candidemia. *Clinical Microbiology and Infection* 2014; **20**: 5-10.
8. Sigera S, Kudavidanage S, Jayasekera P, Jayawardena M, Perera P, H T, *et al*. Candida blood stream infections in Sri Lanka: a retrospective evaluation by the National Mycology Reference Laboratory. 2019.
9. Kotey FC, Dayie NT, Tetteh-Uarcoo PB, Donkor ES. Candida Bloodstream Infections: Changes in Epidemiology and Increase in Drug Resistance. *Infect Dis* (Auckl). 2021; **14**: 117863372110269.