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Short Paper

EpiCandIn: An open online resource for epidemiology of *Candida* infections in India

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***Background & objectives*: *Candida* spp. cause candidiasis in humans under conditions disrupting the host defence. While *Candida albicans* is the most reported cause of candidiasis, there is a surge in the incidence of infections by non-*albicans Candida* species (NACs), such as *C. tropicalis, C. glabrata* and *C. auris*. These species can infect all organs of the human body. To effectively manage these outbreaks, it is important to track the epidemiology of candidiasis. A consolidated resource describing the landscape of candidiasis in India is absent.**

***Methods*: To address this gap, we have developed an online resource named Epidemiology of *Candida* Infections in India (EpiCandIn) by manually curating published literature on *Candida* infections in the Indian population obtained from PubMed and ScienceDirect databases.**

***Results*: EpiCandIn contains data available since 1972 from 51 sites across 16 States and four Union Territories of India. It provides information on geographical location, *Candida* species, niche affected, disease characteristics and drug therapy details extracted from the publications. This resource is integrated with visualization tools.**

***Interpretation & conclusions*: EpiCandIn will be useful for public health researchers and policymakers as it will help them gain insights into the emerging trends and management of *Candida* infections in India. It can be accessed at *epicandin.bicnirrh.res.in*.**

Key words *Candida* - candidiasis - clinical data - database - disease burden - EpiCandIn - epidemiology - India

Candida spp. are commensals colonizing skin and mucosal membranes of oropharyngeal, gastrointestinal and genitourinary tracts of humans[1]. Based on the host's immune status, these opportunistic pathogens can cause localized and systemic infections. Invasive candidiasis is a significant cause of mortality and morbidity in immunocompromised and immunocompetent individuals. Some of the major risk factors for *Candida* infections are prolonged use of antibiotics and hospitalization, diabetes, cancer, HIV/AIDS and immunosuppression associated with transplant recipients[2]. A recent systematic review estimated that

~4.1 per cent of the Indian population, *i.e*., ~60 million people, suffer from a serious fungal disease, including candidiasis[3].

While *Candida albicans* (*C. albicans*) is the most commonly identified infectious species of *Candida* worldwide, there has been a rise in infections caused by non-*albicans Candida* species (NACs). Single and multi-species infections by *Candida* pose a serious public health challenge. Treatment options for managing these infections are limited to a few antifungal drug classes: azoles, polyenes, echinocandins and pyrimidine analogues. The high cost of echinocandins hinders their widespread use in low- and middle- income countries such as India[4,5]. Amphotericin B causes nephrotoxicity; hence, its use is limited mainly to severe cases of invasive candidiasis[6]. This has led to an increased use of fluconazole for candidiasis treatment. This dependence on a limited repertoire of antifungal drugs has led to the emergence of multidrug-resistant species such as *C. glabrata*, *C. krusei* and *C. auris*[7].

The geographical distribution of infection-causing species of *Candida* varies. *C. tropicalis* and *C. parapsilosis* are the most common NACs in Latin America, whereas *C. glabrata* is the most common NAC in North America and in some European countries[8]. *C. auris* infection, which was first reported in Japan, has been subsequently reported in 47 different countries, including India[9]. Age can also influence the type of *Candida* infection. *C. parapsilosis* is more commonly isolated from neonates and infants as compared to adults[10]. Depending on the microenvironment and comorbidities, *Candida* spp. can infect most human body organs, leading to conditions like oropharyngeal candidiasis, vulvovaginal candidiasis or candidemia. Oropharyngeal candidiasis is the most common fungal infection reported in people suffering from HIV/AIDS[11], whereas diabetic females are more likely to suffer from vulvovaginal candidiasis[12].

Candida spp. is a leading cause of nosocomial infections worldwide. Numerous clinical reports related to candidiasis diagnosis, management and outcomes have been published in India. However, this information has not been systematically curated for further analysis. The Centers for Disease Control and Prevention website provides data on *Candida* epidemiology in the American population. ClinEpiDB, an open-access database to explore and visualize epidemiology studies around the world[13], does not contain any information on *Candida* or candidiasis. Other resources for *Candida* include non-epidemiological databases like the Candida Genome Database (CGD) and CandidaDB. CGD is an open online resource containing gene, protein and sequence-related information about multiple species of *Candida*, such as *C. albicans*, *C. auris*, *C. glabrata*[14]. CandidaDB, a database for genomic data on *C. albicans* and other related yeasts, has been discontinued[15]. Currently, no web resources showcase the epidemiology of *Candida* infections in India. To address this gap, we have developed EpiCandIn, an online curated compilation of Indian clinical reports of *Candida* infections.

EpiCandIn was created by manually curating scientific publications from 1972 to 2022 that report the prevalence of *Candida* infections, pathogenic species, organs affected, mode of treatment, mortality and antifungal susceptibility profiles of *Candida* isolates in different geographical locations of India. This resource will be useful for clinicians and policymakers to understand the changing trends of *Candida* infections and design appropriate management strategies.

Material & Methods

The study was undertaken at the Biomedical Informatics Centre, ICMR-National Institute for Research in Reproductive and Child Health, Mumbai, India.

Screening publications for data extraction: PubMed and ScienceDirect databases were searched to obtain articles pertaining to *Candida* research in India published till December 31, 2022. The search query used for PubMed was '((Candida [Title]) OR (Candidemia [Title]) OR (Candidiasis [Title]) OR (Candiduria [Title])) AND ((India [Title/Abstract]) OR (Indian [Title/Abstract]) OR (India [Affiliation]))'. The search query used for ScienceDirect was 'Title: Candida OR Candidemia OR Candidiasis OR Candiduria, Author Affiliation: India'.

The abstracts of all articles were manually curated to include original scientific reports of *Candida* infections in the Indian population. Publications on *Candida* infections for which full text was not accessible were rejected. Publications with inconsistencies in the data reported in different article sections were rejected. Publications reporting non-epidemiology data, epidemiology data from non-Indian patients, data obtained from *in silico*, *in vitro* or *in vivo* models were excluded. The workflow adopted for this study is shown in Figure.

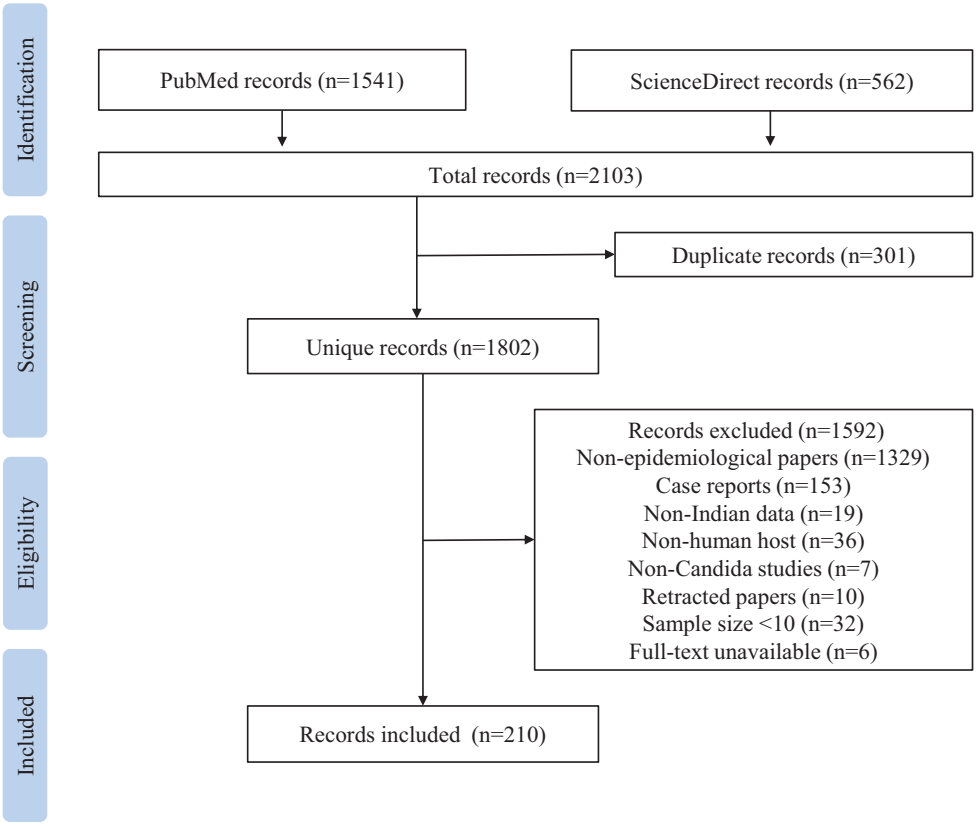

Figure. Flowchart of the literature screening process. Manual review of 2103 records resulted in the selection of 210 eligible publications having clinical data on candidiasis in the Indian population.

Manual curation and data extraction: All the eligible publications were manually curated to extract the following information: author names, publication year, study duration, study design, clinical setup, geographical location, comorbidities, risk factors, species, type of candidiasis, niche infected, symptoms, antifungal drugs prescribed, age and sex of participants, number of patients, number of *Candida* isolates, identification methods, antifungal susceptibility profiles, methods of antifungal susceptibility testing, prevalence, and mortality.

Rules adopted for redundancy elimination in the database are listed in Supplementary Table I. The organs infected with *Candida* spp. and the type of candidiasis was determined as per the collected culture-positive biological samples (Supplementary Table II). The spellings of species names have been corrected as per NCBI Taxonomy database[16]. If a species name was not available in NCBI Taxonomy database, the most frequently used spelling was selected (Supplementary Table III).

Data analysis: Due to a lack of uniformity in the sample collection and reporting methodology, statistical analysis could not be performed on the collated data. Data visualization packages such as ggplot2 library in R software (*cran.r-project.org/web/packages/ggplot2/index.html*) were employed to gain insights from the database.

Database architecture: EpiCandIn is built on Apache HTTP Server 2.4.51 with MySQL Server 5.7.36 as the back-end and PHP 7.4.26, HTML and JavaScript as the front-end. D3.js JavaScript library was used for data visualization.

Results & Discussion

Candidiasis is among the most common nosocomial infections observed in India and globally. The clinical presentation and aetiology of candidiasis are dependent on the medical history, age, organs affected and the geographical area of the individuals[2]. Hence, it is important to assess and comprehend the evolving landscape of *Candida* infections in India. We have compiled clinical data from pan-India reports of *Candida* infections and presented it in a user-friendly online format through EpiCandIn.

EpiCandIn has a simple, user-friendly interface that facilitates navigation through the database. EpiCandIn can be accessed freely at *epicandin.bicnirrh.res.in*. The interface includes search, browse and visualization options for geographical location, species, affected niches and antifungal drugs.

Homepage: The Homepage of EpiCandIn contains an interactive map of India. The geographical sites contributing the data in EpiCandIn are highlighted on the map. Clicking on these sites will provide a tabular view of epidemiology studies and associated details from the selected locations. Quick links to access studies related to individual species, niches and antifungal drugs are also available here.

Search & download: Users can avail the simple or advanced search options to query the database. Simple search is through keyword check on all fields and advanced search functions through query builder wherein keywords are searched based on the specific fields defined by the user. Users can also download the data in a tabular format.

Submit: Through this portal, clinicians and researchers can submit epidemiological data on *Candida* infections from India along with the associated publications. This data will be manually curated and verified for inclusion and subsequent data extraction for EpiCandIn updates.

The literature search yielded 2103 results, comprising 1541 articles from PubMed and 562 articles from ScienceDirect. After removing 301 duplicate articles, the remaining 1802 publications were manually reviewed, and 210 eligible papers were included in the EpiCandIn database. It contains data from 51 sites in 16 States and four Union Territories of India. These studies provide information on 38 unique *Candida* species isolated from 25 different host niches (Supplementary Table II) reported over a span of five decades.

The major challenge during data curation and extraction was the incomplete or missing information in the retrieved publications. The data on geographical location, gender, treatment modalities and outcome were missing in several papers. In the case of studies spanning multiple years, the observations were not segregated year-wise. With respect to age as a parameter, several articles used terms such as 'neonates', and 'reproductive-aged women' without indicating the exact age. A few reports mentioned a broad range of 1–88 yr[17], 0–80 yr[18] and 0–70 yr[19] for the study participants. Notably, we did not find any published clinical reports on candidiasis from Himachal Pradesh, Bihar, Jharkhand and the northeastern States (except Assam).

A limitation of this study is the absence of statistical analysis because of the lack of uniformity in sample collection and data reporting across the publications. These issues have restricted the analytical scope of the data present in EpiCandIn. Therefore, a simple analysis of the data was performed, which revealed the following: *(a) C. albicans* is the most reported species for candidiasis followed by *C. tropicalis*, *C. glabrata* and *C. parapsilosis* (Supplementary Fig. 1 and 2); *(b)* clinical reports on *C. auris* and other NACs increased since 2011 (Supplementary Fig. 1); *(c)* blood was the most well-studied niche followed by the oropharynx and genitourinary tract (Supplementary Fig. 3 and 4); and *(d)* fluconazole was the most widely prescribed antifungal drug, followed by amphotericin B (Supplementary Fig. 5).

We observed a shift from simple microscopic and culture-based methods to more sophisticated molecular techniques such as polymerase chain reaction (PCR), DNA sequencing and matrix-assisted laser desorption/ ionization time-of-flight (MALDI-TOF) mass spectrometry for the detection of *Candida* species over the last two decades. This may have contributed to improved species-level identification, leading to a rise in reports on NACs such as *C. auris* since 2011[20]. These species were identified mostly from the blood, oral cavity and genitourinary tracts (Supplementary Fig. 4), probably due to the ease of sample collection. Candidiasis management heavily depended on fluconazole and amphotericin B (Supplementary Fig. 5). Despite the rise in azole-resistant *Candida* isolates, fluconazole has remained the most widely prescribed antifungal drug for candidiasis in India over the years (Supplementary Fig. 5). This indicates the urgent need for expanding the antifungal therapeutic options through new drugs and targets. The World Health Organization has stressed upon the need for reports and evidence to understand the burden of infections with regard to the prevalence and antifungal resistance to strengthen global health policies[21].

This study is the first step towards developing a unified platform for studying the epidemiological landscape of candidiasis in India. EpiCandIn will enable researchers, clinicians and policymakers to browse the data on Indian clinical reports and draw insights on the increasing burden of *Candida* infections. Periodic updates of this database with clinical data will enable

us to strengthen the candidiasis management strategies in India.

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***Conflicts of Interest*:** None.

***Use of artificial intelligence (AI)-assisted technology for manuscript preparation*:** The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

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