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COVID-19 pandemic and the evolving epidemiology of Candidemia: A topic of concern!!!

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Abstract

Candidemia is the most common recorded invasive fungal infection worldwide. During the last couple of years, the world has been struggling with the COVID-19 pandemic caused by the Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV-2), during which an increase in the incidence of candidemia and *Candida auris* cases were reported by several researchers. This study aimed to address how the entire landscape evolved during the downslide of the COVID-19 pandemic over the study period that spanned five years, including the pre-pandemic, peak, and waning of the COVID-19 pandemic. This retrospective observational study was conducted on a cohort of 1450 tertiary care cases in a University hospital in Jaipur, India, from July, 2017 to November, 2021. During the study period, all blood cultures of the suspected sepsis cases were screened for candidemia. Identification and antifungal susceptibility testing of *Candida* isolates were carried out using the standard assays. A consistent increase in the prevalence of candidemia has been observed during the current study period. Despite this, the prevalence of Non *albicans Candida* has remained almost steady. A sharp increase in *C. auris* candidemia during the COVID-19 pandemic was observed. The waning of the COVID-19 pandemic has brought the epidemiology of candidemia back to the pre-pandemic times, and *C. tropicalis* has become the predominant clinical isolate again. There is a slight fall in resistance to fluconazole. Echinocandins, which is considered as a remedy till few years back, has also showed first signs of emerging resistance in patients attending to Mahatma Gandhi University of Medical Sciences & Technology (MGUMST), Jaipur, Rajasthan, India. Due to the extreme overlapping of the associated disease/ risk factors observed between COVID-19 and candidemia, these two disease entities have definitely influenced the epidemiology of each other's. However, how the landscape will evolve in the aftermath of the COVID-19 pandemic is yet to be detected.

Keywords: Antifungal susceptibility, *Candida auris*, Candidemia, COVID-19 pandemic, Echinocandins

1. Introduction

Advancements in the healthcare sector, especially the oncology and transplant sciences, have resulted in an expanding pool of vulnerable populations, including the elderly and immunocompromised patients. This cohort of population is at risk of hospitalization in the intensive care units (ICUs) for prolonged periods of time, as the hospital's stay is often being compounded by the use of broad-spectrum antibiotics and invasive devices. All these factors collectively produce an ecosystem wherein the invasive fungal infections are becoming more common. Candidemia is the most common invasive fungal infection observed worldwide. It is a major cause of morbidity and mortality among the hospitalized patients, especially in the developing countries (Pfaller and Diekema, 2007; McCarty and Pappas, 2016).

The epidemiology of candidemia is constantly evolving. The shift in the causative species causing candidemia from *C. albicans* to Non *albicans Candida* (NAC) has been documented on a global level (Kaur *et al*., 2020; Alhatmi *et al*., 2022; Gautam *et al*., 2022). New multidrug resistant species such as *C. auris* are being reported in the previous study conducted by Chowdhary *et al*., (2017). There is also an increasing burden of antifungal resistance that needs to be addressed (McCarty and Pappas, 2016; Chowdhary *et al*., 2018; Kordalewska *et al*., 2018). The last couple of years have recorded an unprecedented level of pressure on the healthcare industry. The whole world has been gripped in Coronavirus disease-2019 (COVID-19) pandemic caused by infection with SARS-CoV-2 virus, which continued to show several peaks and troughs. This pandemic has begun in December, 2019 with its epicenter in Wuhan, the capital city of Hubei province in China, and then engulfed the whole world fast. While many nations are recovering from this onslaught, others are still facing fresh waves of this viral infection (Zhu *et al*., 2020a). There has been a massive influx of patients that require critical health care coupled with fallout of infection control practices. Several recent studies have reported an increased incidence of candidemia and the steep rise in *C. auris* cases observed during the COVID-19 pandemic (Rajni *et al*., 2021a; Allaw *et al*., 2022; Ramos-Martínez *et al*., 2022; Routsi *et al*., 2022). It would however be interesting to note how the entire landscape, including the antifungal susceptibility pattern is evolving during the downslide of the COVID-19 pandemic. The objective of this study was to discuss elaborately these disease issues over a study period spanning of 5 years, including the pre-pandemic, peak, and the waning of the COVID-19 pandemic.

2. Materials and methods

2.1. Phases of the study

The entire study has been conducted in 3 phases. The initial pre-pandemic phase stretched over 3 years (July, 2017-June, 2020), and elucidated the baseline epidemiology of candidemia in Mahatma Gandhi hospital (Rajni *et al*., 2022). The second phase spanned over 6 months i.e., August, 2020 to January, 2021, and coincided with the peak of COVID-19 pandemic. Since the onset of the COVID-19 pandemic, the Mahatma Gandhi hospital attached to MGUMST was designated as a COVID-19 care center by the Government of Rajasthan, and operated as an approved high volume COVID-19 treatment center (Rajni *et al*., 2021b). After this, the number of COVID-19 cases declined sharply in Mahatma Gandhi University of Medical Sciences & Technology (MGUMST), Jaipur, Rajasthan, India, and although several restrictions were placed on travelling, hospitalization and commercial institutes; however, they were later relaxed in a phasic manner. The third phase of study deal with waning of the COVID-19 pandemic, and constitute 6 months from June, 2021 to November, 2021, which thereafter had referred to as a post pandemic period.

2.2. Isolation and identification of the *Candida* spp.

This retrospective observational study was conducted on 1450 tertiary care cases in Mahatma Gandhi University of Medical Sciences & Technology (MGUMST), Jaipur, Rajasthan, India, through the period from July, 2017 to November, 2021. The data were collected from an adult ICU complex, which encompassed medicine ICU (22 beds), surgery ICU (8 beds), neuro ICU (14 beds), and a separate unit (10 beds) dedicated for COVID-19 patients and other infectious diseases. During the study period, results of blood cultures of all the suspected sepsis cases were screened for candidaemia (Kullberg and Arendrup, 2015). Candidaemia is defined as isolation of Candida species from blood cultures at least once in the presence of clinical features of sepsis. Only one isolate of Candida sp. per patient was included for the study purpose.

2.3. Antifungal susceptibility assay

Candida species were identified through the Matrix assisted laser desorption/ ionization time-of flight mass spectrometry (MALDI-TOF Bruker Biotyper OC version 3.1, Daltonics, Bremen, Germany, https://www.bruker.com), using the ethanol formic acid extraction protocol of van Veen *et al*., (2010). The antifungal susceptibility testing was performed using the Clinical and Laboratory Standards Institute (CLSI) broth micro-dilution method M 27-A3/S4 of Wayne, (2008); (2020).

2.4. Statistical analysis

Data analysis was performed using SPSS software, version 20 (IBM Corp., USA). The *p*-values < 0.05 were considered as statistically significant.

3. Results

3.1. Characteristics of candidemia and different *Candida* spp.

The salient features of candidemia and distribution of the various *Candida* spp. isolated from blood cultures during the different periods of this study are presented in Tables (1) and (2), respectively. During the pre-pandemic period, out of the 3443 blood cultures that were recorded as positive; candidemia accounted for 95 cases, and the prevalence was 2.8 %. *C. tropicalis* (38 %) was the most common isolate, followed by *C. parapsilosis* (18 %), *C. famata* (12 %), *C. auris*, and *C. albicans* (11 % each), where $p< 0.05$. During the second phase of this study, about 82 % cases of candidemia were attributed to Non *albicans Candida* (NAC); *C. auris* being the most common, which was responsible for 36 % of the recorded cases, as depicted in Table (1 and 2). In the final period of this study (June, 2021- November, 2021), about 811 blood cultures were recorded positive, candidemia was detected in 46 cases, and the prevalence of candidemia was 5.7 %. *C. tropicalis* once again became the most common recovered isolate accounting for 48 % of the cases, while *C. auris* was the next most common recorded species ($p< 0.05$).

3.2. Antifungal susceptibility of the fungal isolates

The antifungal susceptibility pattern of *C. albicans* and NAC, with special reference to *C. auris* over the study period has been summarized in Table (3). For comparison, results of the antifungal susceptibility for the first and third phases of this study were studied in details. During the pre-pandemic period, *C. albicans* isolates were found to be non-resistant (100 % sensitive) to echinocandins; however, resistance to fluconazole, voriconazole, and amphotericin B was observed in 20 %, 10 % and 30 % of the isolates, respectively. Even among the NAC isolates, 100 % sensitivity was recorded for the echinocandins. In the post pandemic period of this study, an increase in resistance for voriconazole, echinocandins (Caspofungin), and amphotericin B has been observed among the NAC isolates, which was found to be statistically significant ($p< 0.05$). Resistance to caspofungin, micafungin, and anidulafungin has been detected in 7.7 %, 2.6 %, and 2.6 % of the NAC isolates, respectively. Notably, resistance to Fluconazole has been reduced from 36 % to 28 %.

Table 1: A summary of salient features of candidemia during the different periods of this study

	July 2017- June 2020 (3years)	**Aug 2020- Jan 2021 (6 months)**	**June 2021- Nov. 2021 (6 months)**
Total blood cultures received from suspected sepsis cases	10800	1166	3685
Total blood cultures reported positive	3443	237	811
No of Candidemia cases detected	95	11	46
Prevalence	2.8 %	4.6 %	5.7 %
Prevalence of NAC*	89 %	82 %	85 %
Most common isolate	*C. tropicalis* (36/95, 38 %)	*C. auris* (4/11, 36 %)	*C. tropicalis* (22/46, 48 %)
Ranking of *C. auris*	4th	1st	2nd
Relative % of *C. auris* cases	(10/95) 11 %	(4/11) 36 %	(8/46) 17 %

Where; *NAC: Non *albicans Candida*

Table 2: Distribution of various *Candida* spp. isolated from blood cultures during the different periods of this study

July 2017- June 2020 (%)	**August 2020-January 2021 (%)**	**June 2021- November 2021 (%)**
C. tropicalis (38 %) *C. parapsilosis* (18 %) *C. famata* (12 %) *C. auris* (11 %) *C. albicans* (11 %) *C. glabrata* (5 %) Others (5 %)	*C. auris* (36 %) *C. tropicalis* (28 %) *C. albicans* (18 %) *C. glabrata* (9 %) *C. parapsilosis* (9 %)	*C. tropicalis* (47 %) *C. auris* (17 %) *C. albicans* (15 %) *C. parapsilosis* (10 %) *C. famata* (4 %) *C. glabrata* (4 %) *C. lusitaniae* (3 %)

Table 3: Comparison of antifungal susceptibility pattern of *C. albicans*, Non *albicans Candida* (NAC), and *C. auris* observed during the different periods of this study

	C. albicans			**NAC**			***C. auris***		
	July, 2017 - June, 2020 N (%)	June, 2021- Nov, 2021 N (%)	*p*-value	July, 2017- June, 2020 N (%)	June, 2021- Nov, 2021 N (%)	*p*-value	July, 2017- June, 2020 N (%)	June, 2021- Nov, 2021 N (%)	*p*-value
FLU	2(20 %)	0(0 %)	0.621	34(40 %)	11(28.2 %)	0.286	9(94 %)	8(100 %)	0.908
VRC	1(10 %)	0(0 %)	0.853	19(22 %)	9(23.1 %)	0.887	4(42 %)	6(75 %)	0.314
CFG	0(0 %)	0(0 %)	-	0(0 %)	3(7.7 %)	0.050	0(0 %)	0(0 %)	-
MFG	0(0 %)	0(0 %)	-	0(0 %)	1 (2.6 %)	0.688	0(0 %)	0(0 %)	-
AFG	0(0 %)	0(0 %)	-	0(0 %)	1(2.6 %)	0.688	0(0 %)	1(12.5 %)	0.908
AMP B	3(30 %)	0(0 %)	0.864	79(8.2 %)	6(15.4 %)	0.000	4(35 %)	6(75 %)	0.314

Where; N: The total number of microorganisms susceptible to a particular antibiotic, FLU: Fluconazole, VRC: Voriconazole, CFG: Caspofungin, MFG: Micafungin, AFG: Anidulafungin, AMP B: Amphotericin B

3.3. Prevalence of candidemia over the different study periods

As shown in Fig. (1), an increase in prevalence of candidemia has been observed during the different study periods, recording 2.8 % from July, 2017-June, 2020, 4.6 % from August, 2020-January, 2021, and 5.7 % from June, 2021- November, 2021 ($p < 0.05$).

3.4. Prevalence of various fungal isolates over the different study periods

On the other hand, the relative percentage of *C. albicans*, NAC, and *C. auris* over the 3 study periods is demonstrated in Fig. (2). The NAC cases had shown a prevalence, recording 89 % in July, 2017-June, 2020, 82 % in August, 2020-January, 2021, and 85 % in June, 2021-November, 2021 ($p < 0.05$).

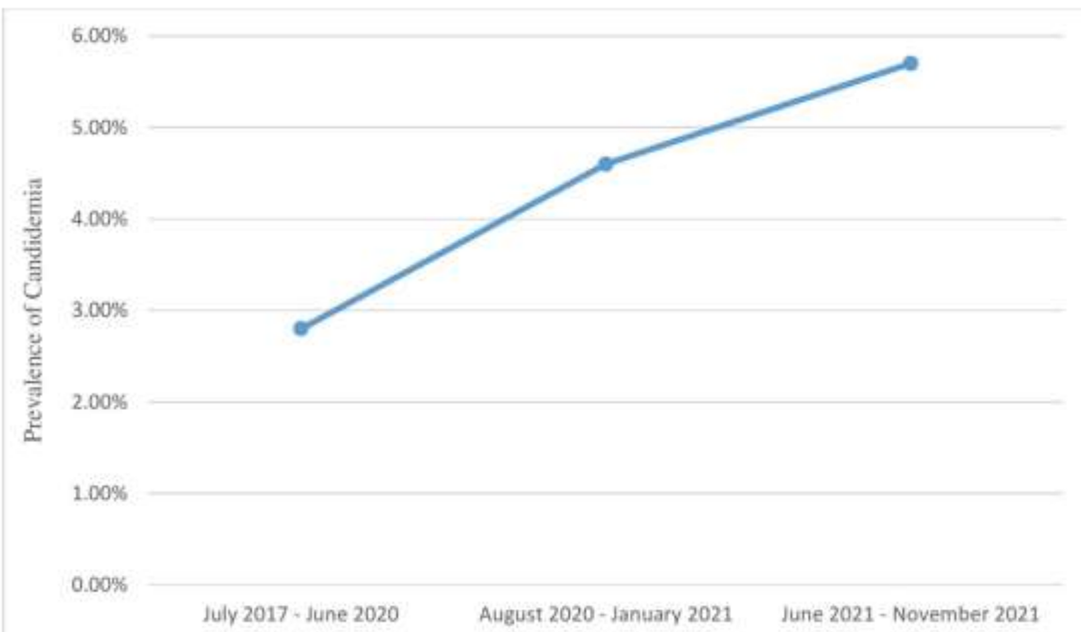

Fig. 1: Increasing trends in prevalence of candidemia over the different periods of the study

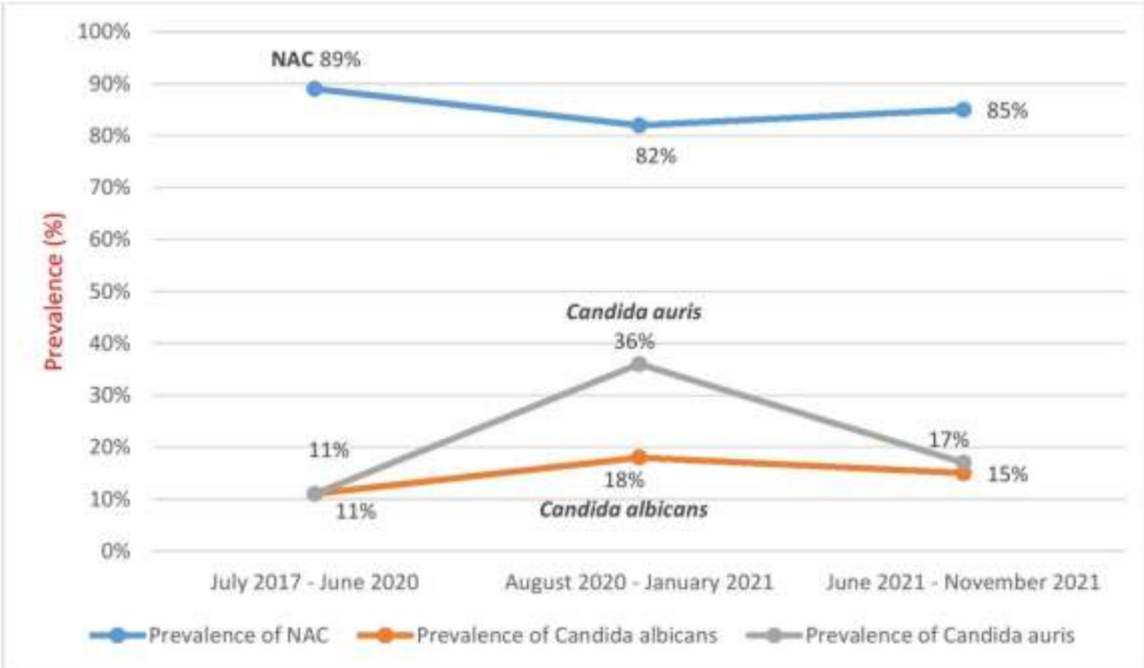

Fig. 2: Prevalence of Non *albicans Candida* (NAC), *C. albicans*, and *C. auris* observed over the different periods of the study

4. Discussion

This study gives an insight into how the COVID-19 pandemic may have influenced the epidemiology of candidemia in Mahatma Gandhi University of Medical Sciences & Technology (MGUMST), Jaipur, Rajasthan, India.

During the pre-pandemic period, the profile of the involved *Candida* spp. was in complete agreement with the other global studies of Kaur *et al*., (2020); Alhatmi *et al*., (2022); Gautam *et al*., (2022), where prevalence of NAC was being much higher than *C. albicans* (89 % vs 11 %).

With the onset of COVID-19 pandemic, a complete state level lock down was declared. The entire hospital infrastructures and manpower were diverted towards catering to the needs of COVID-19 patients. All elective admissions; surgeries, transplant, and oncology services etc. were suspended. Thus, the data collected during the last three months of the first phase of this study (March-June, 2020) may not represent the true burden of candidemia. In fact, in a previous study conducted by Rajni *et al*., (2021b) from March to August, 2020, *C. albicans* was isolated from the blood culture of only a single patient. Nevertheless, till this time, the recorded candidemia cases had shown a steady and consistent rise, where the prevalence being 0.7 % during July, 2017-June, 2018, 0.9 % during July, 2018-June, 2019, and 1.2 % during July, 2019-June, 2020, and this rise was found to be statistically significant ($p < 0.05$).

During the COVID-19 pandemic, the healthcare systems were completely overwhelmed by the huge inflow of Coronavirus disease patients. There were lapses in the routine infection control practices during this period. The indiscriminate use of the broad spectrum antibiotics may have altered the microbiological milieu, thus predisposed the patients to infections with the opportunistic Candida spp. In this study, an increase in the prevalence of candidemia from 2.8 % to 4.6 % was observed. A similar increase in the incidence of candidemia in COVID-19 patients had been highlighted by several recent studies conducted by Riche *et al*., (2020); Shukla *et al*., (2021); Allaw *et al*., (2022); Papadimitriou-Olivgeris *et al*., (2022); Ramos-Martínez *et al*., (2022); Routsi *et al*., (2022).

Candida auris had been increasingly recognized as a serious global health threat (Chowdhary *et al*., 2017). In 2009, *C. auris* was being firstly reported from the ear canal of a patient in Japan; however, increasing numbers of cases are currently reported from all over the world. *C. auris* ability to persist in the environment and causes outbreaks of invasive infections with high mortality rates, in addition to its resistance to the multiple antifungals make this strain a formidable foe for the personnel health (Satoh *et al*., 2009; Kathuria *et al*., 2015; Eyre *et al*., 2018; Zhu *et al*., 2020b).

Even at the beginning of the COVID-19 pandemic, Chowdhary *et al*., (2020) had prophesied that this pandemic may provide "ideal conditions" for outbreaks of *C. auris* in the hospital's ICUs. The horizontal transmission of *C. auris* during the COVID-19 pandemic has been recently documented by Janniger and Kapila, (2021). The healthcare workers hands and/ or shared equipment have been shown to be the vehicles of transmission. In Brazil, a previous study conducted by Nobrega de Almeida Jr *et al*., (2021) revealed that axillary thermometers had facilitated the dissemination of *C. auris* in the COVID-19 ICU's.

During the second phase of this study, and in concordance to its results, a similar increase in incidence of *C. auris* bloodstream infections had been highlighted by several recent studies, including Mastrangelo *et al*., (2021); Villanueva-Lozano *et al*., (2021); Arastehfar *et al*., (2022); Vinayagamoorthy *et al*., (2022). Moreover, a tertiary care center in Lebanon, which was completely naive to *C. auris*, had also experienced its first outbreak of *C. auris* candidemia during this COVID-19 pandemic (Allaw *et al*., 2021). The usage of tocilizumab antibiotic was found to be associated with the development of candidemia in this cohort of critically ill COVID-19 patients (Antinori *et al*., 2020; Morena *et al*., 2020; Rajni *et al*., 2021b). The therapy of all COVID-19 positive symptomatic patients that were suffering from Candida spp. infections, and who were admitted to Mahatma Gandhi hospital was revised and tailored, according to the antifungal susceptibility results provided by the laboratory of the department of Microbiology of Mahatma Gandhi hospital, Jaipur, Rajasthan, India.

Recently, Vinayagamoorthy *et al*., (2022) have given important insight into the conjoint epidemiology of COVID-19 and candidemia. On contrary to the current findings, several previous studies had found that the prevalence of *C. auris* infections remained largely unchanged during the COVID-19 pandemic. Ramos-Martinez *et al*., (2022) from Spain, and Routsi *et al*., (2022) from Greece reported a similar increased incidence of candidemia; however, they found *C. parapsilosis* to be more frequent in the admitted patients suffering from COVID-19. These differences highlight the urgent need to generate and share data about the local epidemiology on a global level.

The period from June, 2021 to November, 2021 pertains to the time when there was a sharp fall in COVID-19 cases and in the case fatality rates. It is noteworthy that the massive influx of COVID-19 patients experienced during the second half of this study had been reduced to the manifold, and the routine hospital services; elective admissions, and surgeries were resumed during this period. The infection control infrastructure that had taken a beat during the COVID-19 peak started to return now to its own self robust. It is possible that adequate usage of personal protective equipment (PPE), and adherence to the infection control measures led to this decline in the *C. auris* cases. Nevertheless, *C. auris* is still currently responsible for around one fifth of the candidemia cases recorded in Mahatma Gandhi hospital. The previous study conducted by Fasciana *et al*., (2020) proposed that screening for *C. auris* colonization should be made as an important part of the admission procedure, thus strengthening the containment efforts. Currently, it is worth mentioning that the infection control practices are firmly in place in Mahatma Gandhi hospital, in addition of being closely monitored.

Echinocandins are recommended as the first line of therapy for candidemia while the susceptibility results are progressing. Although echinocandin resistance has already been reported by several studies, including Chowdhary *et al*., (2018); Kordalewska *et al*., (2018); Maphanga *et al*., (2021); however, in the current study this phenomenon has been observed for the first time in the clinical isolates. Kathuria *et al*., (2015); Kordalewska *et al*., (2018) had previously reported that echinocandin resistance was recorded in 3.8 % and 37 % of the clinical *C. auris* isolates. In another recent study conducted by Sharma *et al*., (2020), 5.5 % of the *C. auris* isolates were recorded to be echinocandin resistant, as the Centers for Disease Control and Prevention (CDCP) had recommended cut-off values. About 4.5% of these isolates were found to be resistant to at least one echinocandin. In this study, resistance to anidulafungin was observed in a single isolate of *C. auris*, which might be attributed to the increased usage of echinocandins as an empirical therapy in candidemia cases during peak of the COVID-19 pandemic.

In the recent systemic review, Vinayagamoorthy *et al*., (2022) revealed that 97 of the *C. auris* cases in COVID-19 patients have recorded resistance to fluconazole; voriconazole, amphotericin B, caspofungin, micafungin, anidulafungin, and 5-fluorouracil in 81 %, 29 %, 46 %, 13 %, 3.7 %, 5 %, and 44 % of the isolates, respectively. Moreover, in the same study, a large number of isolates had been reported to be resistant to voriconazole (14 %-90 %), and amphotericin B (8 %-61 %). Low degree of resistance had been recorded globally for echinocandins (0.5 %- 3 %), as reported previously by several studies of Eyre *et al*., (2018); Zhu *et al*., (2020b); Maphanga *et al*., (2021); Escandon *et al*., (2022). On the contrary to the previous findings presented by Routsi *et al*., (2022), the current study did not witness any rise in Fluconazole resistance. These developments warrant that sharp clinical judgment should be used in prescribing the suitable antifungals, to maintain the sanctity of this group of drugs. Moreover, the Candida isolates need to undergo molecular testing's to determine their specific mechanisms of resistance.

Although the clinicians all over the world were triaging sick COVID-19 patients; however, there was an unchecked use of steroids, in duration and quantity that far exceeded the World Health Organization (WHO) recommendations. This led to an unprecedented surge that was observed in mucormycosis (Singh *et al*., 2021). India with its second largest burden of people living with diabetes in the world faced a severe onslaught of mucormycosis. Usage of the antifungals such as voriconazole and Amphotericin B showed a sharp rise during the COVID-19 pandemic. Whether the rise in antifungal resistance that was observed in this study stem from this increased usage of antifungals or not is hard to pinpoint. At this point, authors of the current study reiterate the importance of judicious use of antifungals in the clinical practices.

Several recent studies conducted by Mastrangelo *et al*., (2021); Arastehfar *et al*., (2022); Ramos-Martinez *et al*., (2022); Routsi *et al*., (2022) have highlighted the risk factors associated with candidemia, especially for *C. auris* infections. Interestingly, severe COVID- 19 infections have been associated with a similar set of risk factors, including diabetes mellitus; chronic liver, malignancies, kidney and heart disease, hypertension, prior usage of antibiotics, prolonged ICU stay, in addition to the presence of invasive devices, such as the central venous catheter and mechanical ventilation, etc. Due to the extreme overlapping of the underlying disease/ risk factors observed between COVID-19 and candidemia diseases, it is difficult to imagine that they will not influence the epidemiology of each other's. At this stage, it is perhaps a little early to make these conclusions, and more detailed studies are needed to evaluate this interaction. While concerns have been raised regarding how the current COVID-19 pandemic may influence the antimicrobial resistance; however, its role in shaping the antifungal resistance also needs pondering (Magnasco *et al*., 2021; Singh *et al*., 2021). Nevertheless, this study clearly describes the current epidemiology of candidemia, especially in backdrop of the rise and control of COVID-19 pandemic.

The strength of the current study lies in the fact that the authors have included all the suspected sepsis cases recorded in the Mahatma Gandhi hospital as a denominator, thereby giving a true picture about the burden of candidemia in this hospital set up. To the best of our knowledge, this is the largest collection of candidaemia cases recorded in the Northern India within the last 5 years, including the COVID-19 pandemic duration.

However, this study has few limitations, as there may have been few confounding factors observed during its retrospective design. During the last few months of the first part of the current study; when complete lockdown was announced, the ensuing confusions and panics regarding the COVID-19 virus may have resulted in a lower rate of samples collection. Furthermore, molecular testing's could not be carried out for the Candida isolates that exhibited echinocandin resistance, and the data pertained to a single center of study.

Conclusion

The conclusions derived from the current study, include that prevalence of candidemia had increased during the COVID-19 pandemic (2.8 % vs 4.6 %), and it continued to increase even after the pandemic had declined. The prevalence of NAC has remained almost steady. A sharp rise was observed in *C. auris* candidemia during the COVID-19 pandemic. The waning of COVID-19 pandemic has brought the epidemiology of candidemia back to the pre-pandemic times, where *C. tropicalis* has again become the most common isolate. There is a notable shift in the antifungal susceptibility profiles of these clinical isolates. Echinocandins, which were considered as panacea till a few years back, are also showing the first signs of emerging resistance in Mahatma Gandhi hospital. However, more studies are required to understand how the epidemiology of candidemia will evolve in aftermath of the COVID-19 pandemic.

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Conflict of interest

The author(s) declare no potential conflict of interests with respect to the research, authorship, and/or publication of this article.

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Ethical approval

This study was granted ethical approval vide letter no. MGMCH/IEC/JPR/2021/552. The need for patients consent was waived, as the study included only retrospective data collection with no interventions.

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