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REVIEW ARTICLE

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Prevalence, risk factors, treatment and outcome of multidrug resistance *Candida auris* infections in Coronavirus disease (COVID-19) patients: A systematic review

Kalaiselvi Vinayagamoorthy[1] | Kalyana Chakravarthy Pentapati[2] | Hariprasath Prakash[3]

[1]Centre for Public Health (U.I.E.A.S.T), Panjab University, Chandigarh, India

[2]Department of Public Health Dentistry, Manipal College of Dental Sciences, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

[3]Medical Microbiology, Department of Public Health, International Higher School of Medicine, Cholpon-Ata, Kyrgyzstan

Correspondence
Dr. Hariprasath Prakash, Medical Microbiology, Department of Public Health, International Higher School of Medicine, Issyk-Kul Regional Campus, Cholpon-Ata 722125, Kyrgyzstan.
Email: harisath2003@gmail.com

Abstract

Background: *Candida auris* is an emerging multidrug-resistant pathogen in intensive care settings (ICU). During the coronavirus disease 19 (COVID-19) pandemic, ICU admissions were overwhelmed, possibly contributing to the *C. auris* outbreak in COVID-19 patients.

Objectives: The present systematic review addresses the prevalence, underlying diseases, iatrogenic risk factors, treatment and outcome of *C. auris* infections in COVID-19 patients.

Methods: MEDLINE, Scopus, Embase, Web of Science and LitCovid databases were systematically searched with appropriate keywords from 1 January 2020 to 31 December 2021.

Results: A total of 97 cases of *C. auris* were identified in COVID-19 patients. The pooled prevalence of *C. auris* infections (encompassing candidemia and non-candidemia cases) in COVID-19 patients was 14%. The major underlying diseases were diabetes mellitus (42.7%), hypertension (32.9%) and obesity (14.6%), followed by the iatrogenic risk factors such as a central venous catheter (76.8%%), intensive care unit (ICU) stay (75.6%) and broad-spectrum antibiotic usage (74.3%). There were no significant differences in underlying disease and iatrogenic risk factors among *C. auris* non-candidemia/colonisation and *C. auris* candidemia cases. The mortality rate of the total cohort is 44.4%, whereas, in *C. auris* candidemia patients, the mortality was 64.7%.

Conclusion: This study shows that the prevalence of *C. auris* infections remains unchanged in the COVID-19 pandemic. Hospital-acquired risk factors may contribute to the clinical illness. Proper infection control practices and hospital surveillance may stop future hospital outbreaks during the pandemic.

KEYWORDS
Candida auris, candidemia, COVID-19, mortality, prevalence, systematic review

1 | INTRODUCTION

During the coronavirus disease 19 (COVID-19) pandemic, the healthcare facility was overwhelmed with patients admitted to intensive care units (ICUs), and those patients were highly susceptible to bacterial and fungal co-infections.[1,2] *Candida auris* is an emerging pathogen in ICU settings with high mortality and infection due to this pathogen has been reported across 44 countries.[3,4] *Candida auris* is a unique species, as this agent is multidrug-resistant, and they can survive on inanimate objects in the hospital environment for more extended periods, leading to potential transmission among patients (hospital outbreaks), and difficulty in accurate laboratory identification makes them the pathogen of public interest globally.[5–8] Patients with underlying diseases such as diabetes mellitus, kidney disease, lung disease, trauma, ear diseases and hypertension, followed by iatrogenic risk factors such as prolonged ICU stay, central venous catheter, mechanical ventilation and prior antibiotic usage, were significantly associated with *C. auris* infections prior to the COVID-19 pandemic.[3,4,9,10]

Like *C. auris* infections, diabetes mellitus, hypertension, malignancies, chronic kidney diseases, chronic liver disease and cardiovascular disease are associated with high mortality in severe COVID-19 patients.[11,12] Underlying disease and the invasive medical procedures during the hospital stay in COVID-19 patients make them highly susceptible to *C. auris* infections/colonisation. The outbreak of *C. auris* infections has been reported during the COVID-19 pandemic across different countries.[13–16] Due to the overlapping features (underlying disease/risk factors) between the two disease groups, the disease epidemiology of *C. auris* infections in COVID-19 patients will be interesting to study. In the present study, we systematically reviewed the *C. auris* infections/colonisation in COVID-19 patients to determine the prevalence, underlying disease/risk factors, treatment and outcome.

2 | METHODOLOGY

2.1 | Literature search and eligibility criteria

The proposal for the present systematic review was registered with PROSPERO (registration number: CRD42021252484). The systematic review was conducted as per PRISMA guidelines. The following databases (MEDLINE, Scopus, Embase, Web of Science, LitCovid, back-reference of the manuscripts) were searched for articles published in the English language from 1 January 2020 to 31 December 2021. The study design is described in Figure 1. Studies encompassing details of *C. auris* infection in COVID-19 patients, such as case reports, case series (≥2 cases), retrospective cohort studies

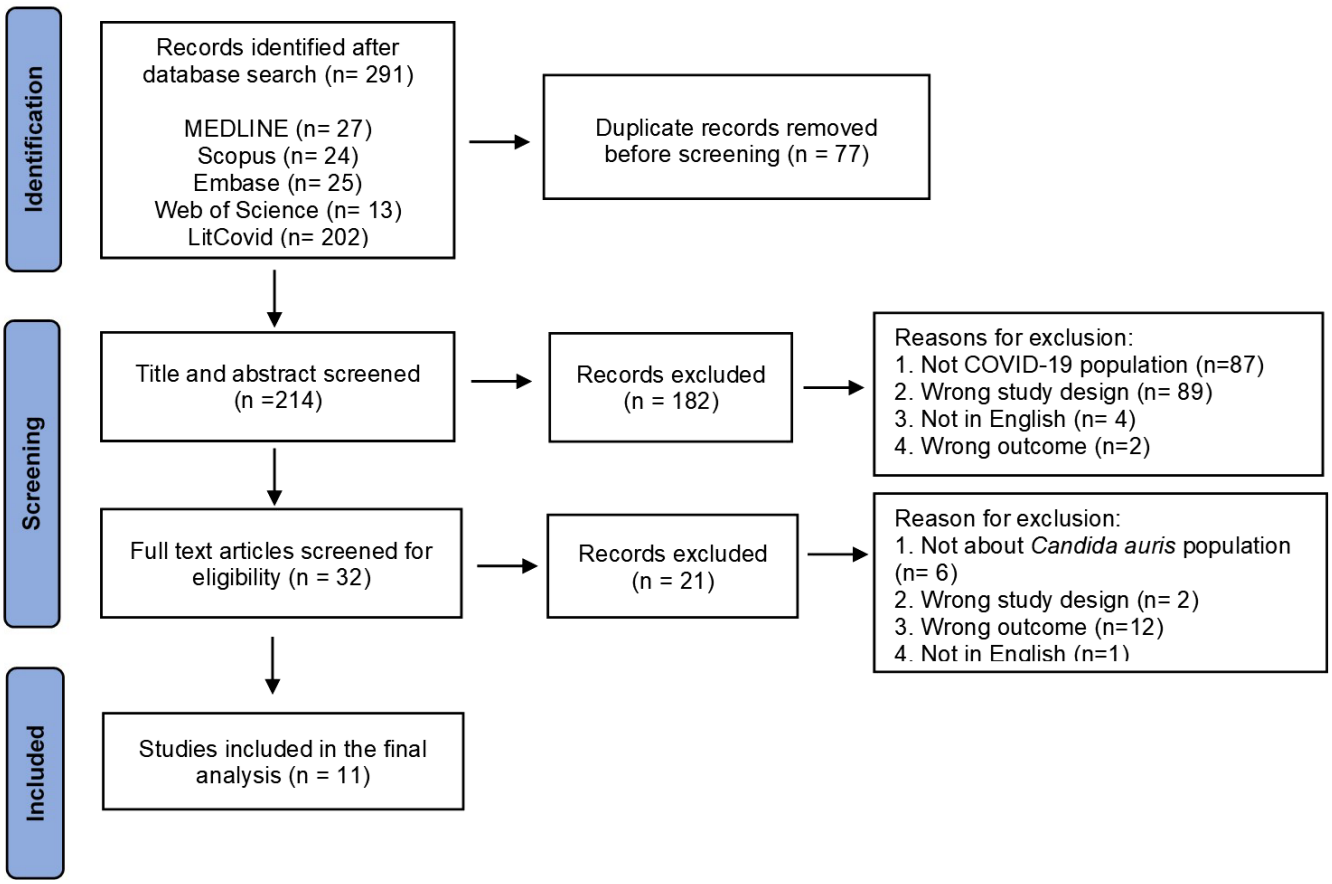

FIGURE 1 PRISMA flowchart describing the study selection process

and observational studies, were included in the review. Studies that failed to fulfil the inclusion criteria were excluded (infections other than *C. auris*, review articles, articles other than English and studies without details of the study population were excluded from the review).

2.2 | Study selection and data extraction

After the literature search, the citations were uploaded to Rayyan QCRI software for screening.[17] Following duplicates removal, the title and abstract of the articles were screened for inclusion by two independent reviewers (KSV and HPP), and disparities were sorted by discussion and consensus (sought the opinion of third reviewer KCP); the qualified articles were screened for full text by two independent reviewers (KSV and HPP). Only the studies that qualified after full-text screening were proceeded to the data extraction process by two independent reviewers (KSV and HPP) and verified by a third reviewer (KCP). The following data were extracted in Microsoft excel: study design, country of the study, number of *C. auris* cases reported, patients details such as age, sex, underlying diseases, iatrogenic risk factors, antifungal treatment and outcome, that is, mortality, details of clinical specimens, antifungal susceptibility results and drug-resistance of the *C. auris* isolates. Further, for estimation of pooled prevalence of *C. auris* infections in COVID-19 patients, only the studies that provided information on total number of *C. auris* cases and total number of COVID-19 cases were included in the analysis (studies without denominators such as case reports and case series were excluded from the prevalence estimation analysis).

2.3 | Risk of bias assessment

The risk of bias assessment was done by two independent reviewers (KSV and HPP) using a modification of the Joanna Briggs Institute (JBI) tool for the case series.[18,19] The risk of bias was assessed as low, high and unclear under the following domains: clear inclusion criteria, a valid identification method, clear reporting of the demographic information, clinical parameters, outcomes, the presenting site(s)/clinic(s) demographic information.

2.4 | Statistical methods

Comparison of underlying diseases, iatrogenic risk factors, antifungal therapy and the outcome of the disease between the *C. auris* non-candidemia/colonisation and *C. auris* candidemia cases was performed using Fisher's exact test using MedCalc Statistical Software (MedCalc Statistical Software version 14.8.1 (MedCalc Software by, Ostend, Belgium; http://www.medcalc.org; 2014)). '*p*' values <.05 was considered significant. Meta-analysis was done using OpenMeta analyst software (version 10.10).[20,21] Pooled prevalence was calculated using the binary random effect model (Restricted Maximum likelihood method). Heterogeneity among the studies was evaluated using I^2 statistics.

3 | RESULTS

The initial database search identified 291 articles; of those, 11 articles were included in the final analysis (Figure 1), and the data were extracted for qualitative and quantitative analysis. Quality assessment of the articles was done using the JBI tool; of the 11 articles assessed, 8 fulfilled the criteria as mentioned above,[13,14,16,22–26] in 3 of the articles, the method of identification was unclear, and the rest of the criteria were fulfilled.[15,27,28] A total of 97 cases of *C. auris* were identified in COVID-19 patients across different countries (Figure 2). Majority of the cases were reported from the United States of America (*n* = 48, 49.5%), followed by Mexico (*n* = 12, 12.4%) and India (*n* = 10, 10.3%; Figure 2). The male to female ratio was 2.6:1. The mean age was 65.41 years (with a range of 1–101 years), and 99% (*n* = 96) of the patients with *C. auris* infections were adults (Table 1). For estimation of pooled prevalence of *C. auris* infections in the COVID-19 patients, the data from the 5 studies were analysed (Figure 3).[15,16,23,25,26] The prevalance of *C. auris* infections (including candidemia and non-candidemia cases) among the COVID-19 patients was 14%, with high heterogeneity among the included publications (I^2 = 99.88; Figure 3).

3.1 | Clinical specimens, isolation and identification of *Candida auris*

Of those 97 *C. auris* cases identified, 62 (64%) patients had details of clinical specimens from which *C. auris* was isolated. Majority of *C. auris* isolation was from blood (*n* = 35, 56.5%), followed by urine (*n* = 12, 19.4%), and respiratory specimens (*n* = 10, 16.1%) (Table 1). The identification of *C. auris* in seven studies was performed using matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS); four studies additionally used DNA sequencing of the internal transcribed spacer (ITS) region for confirmation. Whereas one study used API 20C AUX system (bioMerieux) and phenotypic methods for identification, and in three studies, method of identification is not mentioned.

As per the Center for Disease Control (CDC) (https://ndc.services.cdc.gov/case-definitions/candida-auris-2019/), the case definition of *C. auris* infections/colonisation was specimens collected from invasive infections (eg blood, cerebrospinal fluid) were designated as confirmed cases, whereas isolation of *C. auris* from non-invasive sites (wound swabs, urine and the respiratory tract) may reflect colonisation and not true infection.[29] Based on the definition, in the present study, *C. auris* cases (*n* = 62) were grouped into the following: (a) *C. auris* candidemia (CAC) cases (*n* = 35, 56.5%), (b) *C. auris* non-candidemia/colonised (CANC) cases (*n* = 27, 43.5%; Table 1). The mean days from admission to the first isolation of *C. auris* in CANC and CAC cases were 27.7 and 22.8 days, respectively (Table 1).

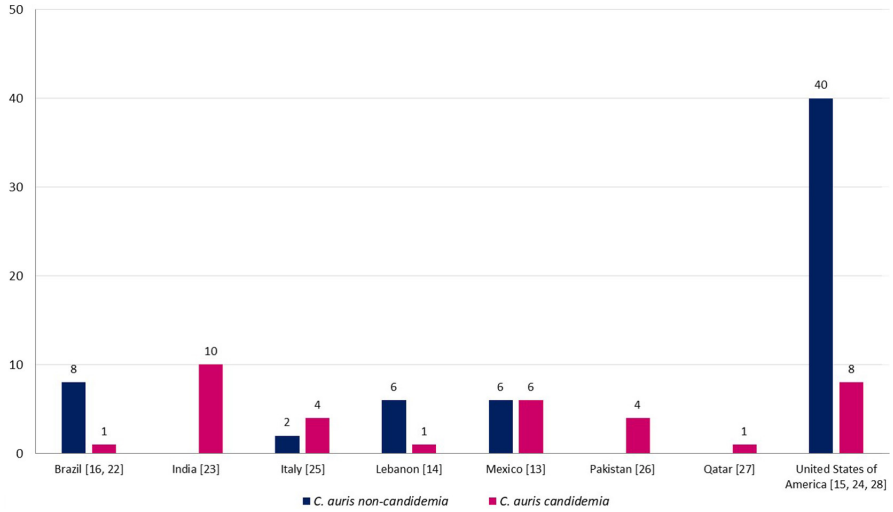

FIGURE 2 *Candida auris* cases in COVID-19 patients across countries. References are given in square brackets

3.2 | Underlying disease and risk factors

Table 1 shows the underlying diseases associated with *C. auris* infections in COVID-19 patients: diabetes mellitus (n = 35, 42.7%), hypertension (n = 27, 32.9%, obesity (n = 12, 14.6%), COVID-19 associated acute respiratory distress syndrome (ARDS; n = 9, 11%) and malignancy (n = 8, 13.4%). Approximately 12% of the patients had no underlying disease. Further, CANC and CAC cases showed no significant differences with any underlying diseases analysed (Table 1). The pooled estimates of the underlying disease and iatrogenic risk factors of *C. auris* infections in COVID-19 patients are depicted in Table 2.

Similar to underlying diseases, iatrogenic risk factors such as central venous catheter (n = 63, 76.8%), intensive care unit (ICU) stay (n = 62, 75.6%), broad-spectrum antibiotic usage (n = 61, 74.3%), mechanical ventilation (n = 57, 69.5%), steroid therapy (n = 51, 62.2%) and urinary catheter (n = 47, 57.3%) showed no significance differences between the CANC and CAC groups. (Table 1). The pooled estimates of co-infections in *C. auris* among the total cohort of COVID-19 patients was 58% (with high heterogeneity I^2 = 88.65) (Table 2).

3.3 | Antifungal therapy and outcome of *Candida auris* infections

A total of 44 patients received antifungal therapy (Table 1); echinocandins (n = 33, 75%) were commonly used, followed by amphotericin B (n = 13, 29.6%). No significant difference was observed between different antifungal medications and the survival (data not shown). The mortality rate of the total cohort (n = 81) was at 44.44% (Table 1), in comparison with CANC cases was at 22.2% (n = 6) and CAC case was at 64.7% (n = 22) (p = <.002). The pooled survival estimates of 61 patients in CANC and CAC groups were 37% and 16%, with low heterogeneity (I^2 = 40.36 and 0%), respectively (Figure 4). The mortality rate in patients with underlying disease and iatrogenic risk factors such as diabetes mellitus, central venous catheter, ICU stay, broad-spectrum antibiotic usage, mechanical ventilation, steroid therapy and urinary catheter were significantly associated with a higher mortality rate in the CAC group compared with the CANC group (Table 3).

3.4 | Antifungal susceptibility of *Candida auris* isolates from COVID-19 patients

Table 4 shows the antifungal susceptibility testing of *C. auris* isolates (n = 41). Of those tested isolates, resistance was noted in 33 isolates (80.5%) to fluconazole (MIC ≥ 32 mg/L), followed by 19 (46.3%) to amphotericin B (MIC ≥ 2 mg/L), 5 (12.8%) to caspofungin (MIC ≥ 2 mg/L), 2 (5.1%) to anidulafungin (MIC ≥ 4 mg/L), 1 (3.7%) to micafungin (MIC ≥ 4 mg/L), and 7 (43.8%) to 5-flucytosine (MIC ≥ 32 mg/L). Voriconazole non-susceptibility (MIC ≥ 2 mg/L) was observed in 12 (29.3%) *C. auris* isolates (Table 4).

Furthermore, 8 (19.5%) isolates were resistant to fluconazole and voriconazole. Multidrug resistance (resistance to two different classes of antifungal drugs) was noted in 22 (53.6%) *C. auris* isolates; of those, 18 (81.8%) and 4 (18.2%) isolates were resistant to two and three classes of antifungal drugs, respectively. Amphotericin B plus azole resistance was noted in 10 (45.5%), followed by echinocandins and azole (n = 4, 18.2%), azole and 5-flucytosine (n = 3, 13.6%), amphotericin B and echinocandins (n = 1, 4.6%), amphotericin B, azole and 5-flucytosine (n = 3, 13.6%) and echinocandins, azole and 5-flucytosine (n = 1, 4.6%).

4 | DISCUSSION

The present systematic review analysed the published cases of *C. auris* in COVID-19 patients, providing insight on prevalence, underlying disease/risk factors, treatment and disease outcome. The review was conducted per PRISMA guidelines, including only the articles that met the study criteria. This review has provided an update on the epidemiology of *C. auris* infections in COVID-19 patients.

TABLE 1 Risk factors, treatment and outcome of *Candida auris* cases in COVID-19 patients

Study Parameters	Total cohort (TC) of Patients [*n* (%)][a]	*Candida auris* non-candidemia (CANC) cases in COVID-19 patients	*Candida auris* candidemia (CAC) cases in COVID-19 patients	*p* value
Candida auris in COVID-19 patients	97 (100)	62	35	-
Age in years (range)	1–101	36–89[b]	1–86[b]	-
Mean age (in years) (*n* = 58)[c]	65.41[c]	65.6[c]	65.3[c]	-
Male:Female ratio (*n*)	2.6:1 (70:27)	3.5:1 (21:6)[b]	4:1 (28:7)[b]	-
Paediatric	1	0[b]	1[b]	-
Adult	96	27[b]	34[b]	-
Mean days from admission to first isolation of *Candida auris* (*n* = 58)[c]	25.1[c]	27.7[c]	22.8[c]	-
	The values are expressed in numbers and percentage [*n* (%)]			
Clinical Specimens and *Candida auris* Isolation[b]	**TC (*n* = 62)[b]**	**CANC Cases (*n* = 27)[b]**	**CAC cases (*n* = 35)[b]**	***p* value**
Blood	35 (56.5)	0	35 (100)	-
Urine	12 (19.4)	10 (37.0)	2 (5.7)	-
Deep tracheal aspirate and broncho alveolar lavage	10 (16.1)	9 (33.3)	1 (2.9)	-
Axillae	6 (9.7)	6 (22.2)	0	-
Groin	5 (8.1)	5 (18.5)	0	-
Skin swab and wound specimens	5 (4.8)	3 (11.1)	2 (5.7)	-
Nostrils	3 (4.8)	3 (11.1)	0	-
Central venous catheter tip	3 (4.8)	2 (7.4)	1 (2.9)	-
Ear swab	2 (3.2)	2 (7.4)	0	-
Underlying diseases	**TC (*n* = 82)[a]**	**CANC cases (*n* = 27)[b]**	**CAC cases (*n* = 35)[b]**	***p* value**
Diabetes mellitus	35 (42.7)	11 (40.7)	12 (34.3)	.79
Hypertension	27 (32.9)	10 (37)	17 (48.6)	.44
Obesity	12 (14.6)	8 (29.6)	4 (11.4)	.106
Immunocompetent	10 (12.2)	2 (7.4)	4 (11.4)	.689
COVID-19 associated acute respiratory distress syndrome (ARDS)	9 (11)	6 (22.2)	3 (8.6)	.16
Malignancy	8 (13.4)	3 (11.1)	2 (5.7)	.645
Renal diseases[d]	11 (13.4)	2 (7.4)	6 (17.1)	.447
Heart disease[e]	8 (9.6)	3 (11.1)	4 (11.4)	>.99
Liver and biliary disease[f]	4 (4.9)	1 (3.7)	3 (8.6)	.626
Thromboembolic disease[g]	5 (6.1)	3 (11.1)	2 (5.7)	.645

(Continues)

TABLE 1 (Continued)

Underlying diseases	TC ($n = 82$)[a]	CANC cases ($n = 27$)[b]	CAC cases ($n = 35$)[b]	p value
Miscellaneous respiratory diseases[h]	9 (11)	5 (18.5)	4 (11.4)	.485
Others[i]	15 (18.3)	7 (25.9)	4 (11.4)	.185
Iatrogenic risk factors	**TC ($n = 82$)[a]**	**CANC cases ($n = 27$)[b]**	**CAC cases ($n = 35$)[b]**	**p value**
Central venous catheter	63 (76.8)	19 (70.3)	28 (80)	.551
Intensive care unit (ICU) stay	62 (75.6)	27 (100)	33 (94.3)	.5
Broad spectrum antibiotic usage	61 (74.3)	26 (96.3)	35 (100)	.436
Mechanical ventilation	57 (69.5)	22 (81.5)	24 (86.6)	.381
Steroid therapy	51 (62.2)	24 (88.9)	27 (77.1)	.321
Urinary catheter	47 (57.3)	17 (63)	19 (54.3)	.606
Co-infections along with *C. auris*	43 (52.4)	13 (48.1)	25 (71.4)	.12
Previous antifungal exposure	19 (23.2)	12 (44.4)	7 (20)	.053
Haemodialysis	7 (8.5)	3 (11.1)	4 (11.4)	>.99
Antifungal therapy[b]	**TC ($n = 62$)[b]**	**CANC cases ($n = 27$)[b]**	**CAC cases ($n = 35$)[b]**	**p value**
Patients received antifungal therapy[j]	44 (71)	11 (40.7)	33 (94.3)	<.001*
Micafungin	16 (25.8)	1 (3.7)	15 (42.6)	<.001*
Caspofungin	14 (22.6)	4 (14.8)	10 (28.6)	.235
Amphotericin B	13 (21)	0	13 (37.1)	-
Anidulafungin	9 (14.5)	4 (14.8)	5 (14.3)	>.99
Voriconazole	8 (12.9)	2 (7.4)	6 (17.1)	.447
Isavuconazole	3 (4.8)	2 (7.4)	1 (2.9)	.575
Fluconazole	3 (4.8)	0	3 (8.6)	-
Clinical outcome	**TC ($n = 81$)[a]**	**CANC cases ($n = 27$)[b]**	**CAC cases ($n = 34$)[b]**	**p value**
Survived	45 (55.6)	21 (77.8)	12 (35.3)	.002*
Death	36 (44.4)	6 (22.2)	22 (64.7)	

Note: The values in the table are expressed in numbers (n) and percentages (%). * 'p' values <.05 were considered significant.

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; CAC, *Candida auris* candidemia; CANC, *Candida auris* non-candidemia/colonised; TC, total cohort.

[a]The data were extracted from the 11 studies which fulfilled inclusion criteria (TC).[13–16,22–28]

[b]Age range, male/female ratio, details of clinical specimens, underlying disease, iatrogenic risk factors, antifungal therapy and clinical outcome of CANC and CAC cases were extracted from 10 studies.[13,14,16,22–28]

[c]Mean age and mean days from first isolation of *C. auris* from admission for CANC and CAC cases were extracted from 9 studies.[13–16,23–25,27,28]

[d]Renal diseases were chronic kidney disease (CKD) and acute kidney injury (AKI). [TC: CKD ($n = 9$), and AKI ($n = 2$); CANC cases: CKD ($n = 2$); CAC cases: CKD ($n = 4$) and AKI ($n = 2$)].

[e]Heart diseases were ischemic heart disease (IHD) and coronary heart disease (CAD). [TC: IHD ($n = 5$), and CAD ($n = 3$); CANC cases: IHD ($n = 2$), and CAD ($n = 1$); CAC cases: IHD ($n = 2$) and CAD ($n = 2$)].

[f]Liver and Biliary diseases were chronic liver disease (CLD) and biliary lithiasis (BL). [TC: CLD ($n = 3$), and BL ($n = 1$); CANC cases: BL ($n = 1$); CAC cases: CLD ($n = 3$)].

TABLE 1 (Continued)

[g]Thromboembolic diseases were pulmonary embolism (PE) and deep venous thrombosis (DVT). [TC: PE ($n = 3$), and DVT ($n = 2$); CANC cases: PE ($n = 1$), and DVT ($n = 2$); CAC cases: PE ($n = 2$)].

[h]Miscellaneous respiratory diseases were asthma, chronic obstructive pulmonary disease (COPD), respiratory failure (RF) and pneumothorax (PT). [TC: asthma ($n = 4$), COPD ($n = 3$), RF ($n = 1$), and PT ($n = 1$); CANC cases: asthma ($n = 1$), COPD ($n = 2$), RF ($n = 1$), and PT ($n = 1$); CAC cases: asthma ($n = 3$), and COPD ($n = 1$)].

[i]Other risk factors included wound infections (WI), hyperlipidaemia (HLD), hypothyroidism (HT), stroke, dementia, stem cell transplant (SCT), systemic lupus erythematosus (SLE). [TC: WI ($n = 6$), HLD ($n = 3$), HT ($n = 2$), stroke ($n = 1$), dementia ($n = 1$), SCT ($n = 1$), and SLE ($n = 1$); CANC cases: WI ($n = 2$), HLD ($n = 1$), HT ($n = 1$), stroke ($n = 1$), dementia ($n = 1$), and SLE ($n = 1$); CAC cases: HLD ($n = 2$), HT ($n = 1$), and SCT ($n = 1$).

[j]In patients with antifungal therapy, many patients received combination of antifungals for treatment.

In the present study, majority of the *C. auris*-infected patients were adults (99%), with one case in the paediatric population, similar to previous reports.[4,6,10] In this study, the pooled prevalence of *C. auris* infections in COVID-19 patients was 14%. The true prevalence of *C. auris* infections in the global population is largely unknown. As per multiple studies, the prevalence of *C. auris* in candidemia patients (non-COVID-19 cases) ranges between 5-30%.[30] Further, many *C. auris* colonisation patients have also been identified in countries like the USA, Europe, India, South Africa and henceforth.[5,31–33]

As per CDC recommendation on *C. auris* definition for colonisation (non-invasive sites) and true infections (invasive sites),[29] in the present study, the cases were classified as *C. auris* non-candidemia/colonised (CANC) and *C. auris* candidemia (CAC) cases, respectively. A total of 35 (56.5%) CAC cases and 27 (43.5%) CANC cases were identified. The underlying disease/iatrogenic risk factors in identified both groups were: hypertension (43.5%), diabetes mellitus (37%), obesity (19.4%), COVID-19-associated ARDS (14.5%) and renal diseases (13%); whereas the iatrogenic risk factors included broad-spectrum antibiotic usage (98.4%), ICU stay (97%), steroid therapy (82.3%), the central venous catheter (75.8%), mechanical ventilation (74.2%) and steroid therapy (82.2%). The respective analysis of *C. auris* and COVID-19 patients showed that both groups shared the underlying disease mentioned above.[3,4,9–12] Multiple studies have reported central venous catheter, previous antifungal exposure, mechanical ventilation, and prolonged ICU stay as significant risk factors for *C. auris* colonisation/infection.[7,34,35] Thus, the ongoing COVID-19 pandemic would become a perfect battlefield for outbreaks of *C. auris* because of the similar underlying diseases and the risk factors, which increases the chance of *C. auris* infections in COVID-19 patients. Further, a recent study from India confirmed these findings, that the treatment with interleukin-6 antagonists such as tocilizumab, prolonged ICU stay, mechanical ventilation and raised ferritin levels were identified as significant risk factors of candidemia (majority of reported cases in the study were due to *C. auris*) in COVID-19 patients.[36]

Furthermore, during the COVID-19 pandemic, the existing ICU facilities have seen overflowing patients, with a high burden of patients, there was a challenge in implementing the infection control practices. Of the included studies in this review, a few studies documented the source for the *C. auris* outbreak, and the infection prevention and control (IPCs) measures to contain the *C. auris* infection in COVID-19 patients.[13,14,16] Allaw et al. reported *C. auris* outbreak in Lebanon in a tertiary care centre for 13 weeks. Following the first case of *C. auris* infection, IPC practices such as hand hygiene using antiseptics, disinfection of floors and surfaces of patient's room, screening for *C. auris* in environmental samples and skin colonisation in patients, 4% chlorhexidine bath for *C. auris* skin decolonisation was initiated. *C. auris* was not isolated from environmental samples; however, of the 26 patients screened for skin colonisation, one patient grew *C. auris*. Authors attributed the delay in reporting and identifying the first case of *C. auris* to the outbreak, which delayed the implementation of IPC measures.[14] Villanueva-Lozano et al.

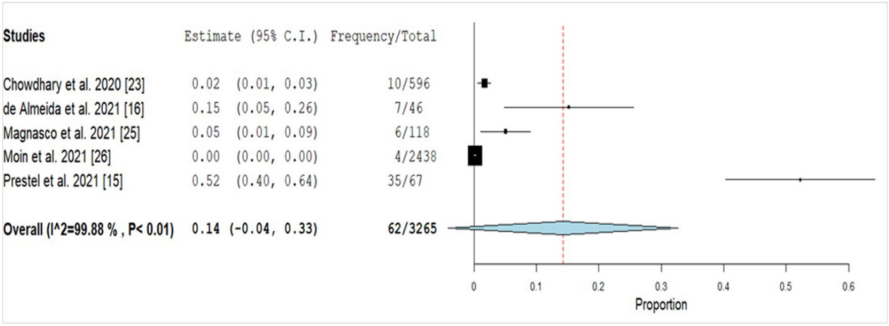

FIGURE 3 Forest plot of pooled prevalence of *Candida auris* infections in COVID-19 patients. "Frequency" denotes total number of *C. auris* cases and "Total" denotes total number of COVID-19 infected patients. References are given in square brackets. Abbreviations: C.I, Confidence Interval

TABLE 2 Pooled estimates of underlying diseases and iatrogenic risk factors of *Candida auris* infections in COVID-19 patients

	Total cohort[a]		*Candida auris* non-Candidemia (CANC)[b]		*Candida auris* Candidemia (CAC)[b]	
Underlying diseases	**Estimate (95% CI)**	**I^2**	**Estimate (95% CI)**	**I^2**	**Estimate (95% CI)**	**I^2**
Diabetes Mellitus	0.38 (0.21–0.51)	59.32	0.16 (0.06-0.25)	22.76	0.17 (0.07-0.27)	33.81
Hypertension	0.33 (0.16–0.5)	77.67	0.31 (0.15-0.47)	0	0.41 (0.22 –0.6)	41.13
Obesity	0.16 (0.03–0.3)	78.73	0.11 (0.04–0.18)	0	0.07 (0.01-0.13)	0
Immunocompetent	0.09 (0.03–0.15)	0.01	0.07 (0.08–0.12)	0	0.06 (0.01–0.12)	0.01
COVID-19 associated acute respiratory distress syndrome (ARDS)	0.23(0.04-0.42)	93.6	0.07 (0.02-0.12)	0.06	0.06 (0.01-0.12)	0.03
Malignancy	0.09 (0.03-0.14)	0	0.07 (0.01-0.13)	0	0.07 (0.01-0.12)	0
Renal diseases[c]	0.12 (0.05–0.19)	0	0.06 (0.01–0.11)	0	0.1 (0.03–0.17)	0
Heart diseases[c]	0.08 (0.03–0.14)	0	0.07 (0.01–0.13)	0	0.08 (0.02-0.14)	0
Liver and biliary disease[c]	0.05 (0.01–0.09)	0	0.06 (0–0.11)	0	0.07 (0.01–0.12)	0
Thromboembolic disease[c]	0.05 (0.01–0.1)	0	0.07 (0.01–0.13)	0	0.07 (0.01–0.13)	0
Miscellaneous Respiratory Diseases[c]	0.1 (0.03-0.16)	16.11	0.09 (0.02-0.16)	0	0.07 (0.01-0.13)	0
Others[c]	0.16 (0.07–0.24)	36.39	0.08 (0.02–0.15)	0	0.09 (0.02 –0.15)	0.02
Iatrogenic risk factors						
Central venous catheter	0.74 (0.56–0.93)	88.54	0.33 (0.11–0.55)	89.79	0.47 (0.24–0.71)	88.07
Intensive Care Unit (ICU) stay	0.81 (0.62–1)	94.08	0.43 (0.22–0.65)	83.6	0.54 (0.32–0.75)	80.94
Broad spectrum antibiotics	0.8 (0.61–1)	93.83	0.41 (0.19–0.63)	84.77	0.59 (0.35–0.79)	83.6
Mechanical ventilation	0.69 (0.5–0.87)	84.45	0.34 (0.15–0.53)	77.44	0.38 (0.21–0.56)	69.15
Steroid therapy	0.68 (0.46–0.91)	93.94	0.39 (0.16–0.61)	87.09	0.43 (0.23–0.64)	77.47
Urinary catheter	0.54 (0.3–0.8)	94.2	0.29 (0.09–0.5)	86.22	0.32 (0.1–0.55)	90.62
Co-infections along with *C. auris*	0.58 (0.36–0.8)	88.64	0.18 (0.06 –0.29)	48.99	0.45 (0.25–0.65)	77.93
Previous antifungal therapy	0.36 (0.13–0.59)	94.87	0.24 (0.05–0.43)	85.78	0.2 (0.02–0.38)	86.14
Haemodialysis	0.07 (0.02–0.12)	8.8	0.06 (0.01–0.11)	0	0.07 (0.01–0.13)	0

Abbreviations: ARDS, acute respiratory distress syndrome; CAC, *Candida auris* candidemia; CANC, *Candida auris* non-candidemia/colonised; CI, confidence interval.

[a]The data were extracted from the 11 studies which fulfilled inclusion criteria (Total cohort).[13–16,22–28] The denominators used in the analysis for the total cohort are $n = 82$.

[b]The data for underlying diseases and iatrogenic risk factors of CANC and CAC cases were extracted from 10 studies.[13,14,16,22–28] Denominators used in the analysis for comparison of CANC and CAC group is $n = 62$.

[c]Refer to Table 1 for the different risk factors placed under the subheadings, such as renal, heart, liver, thromboembolic, miscellaneous respiratory disease and other risk factors.

reported *C. auris* outbreak in COVID-19 patients in Mexico, and the authors isolated three environmental isolates from their bedrooms. The phylogenetic analysis of the clinical and environmental isolates clustered together, suggesting close similarities among the isolates.[13] These findings show that the environmental contamination of hospitals remains a possibility either by cross-contamination of

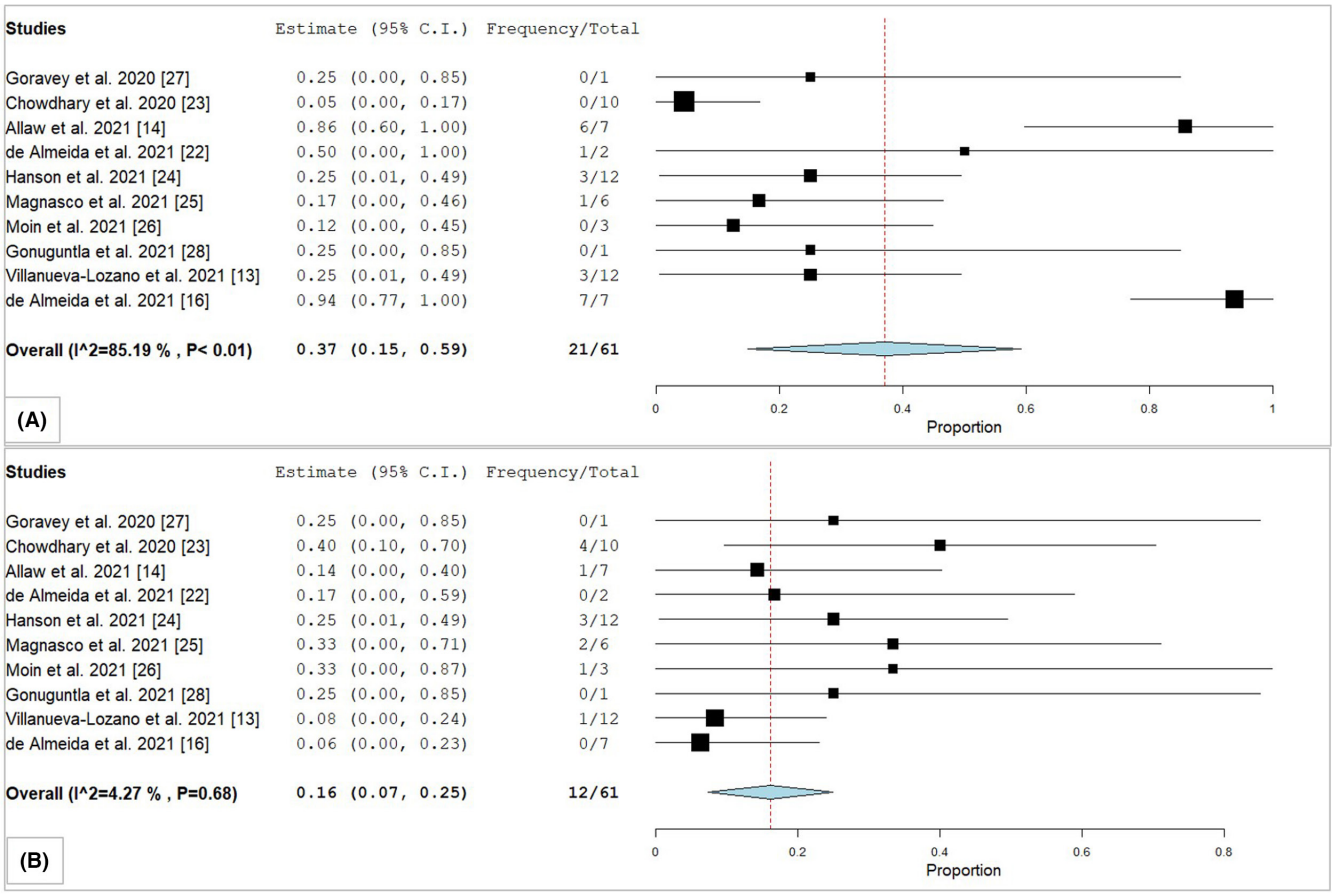

FIGURE 4 Forest plot of pooled survival estimates of (A) *Candida auris* non-candidemia/colonised (CANC) and (B) *Candida auris* candidemia (CAC) cases in COVID-19 patients. "Frequency" denotes total number of patients survived with *C. auris* infections and "Total" denotes total number of *C. auris* cases reported in each study. References are given in square brackets. Abbreviations: C.I, Confidence Interval

TABLE 3 Underlying disease and iatrogenic risk factors associated with mortality in *Candida auris* non-candidemia/colonised (CANC) and *Candida auris* candidemia (CAC) cases

Underlying disease[a] and Iatrogenic risk factors	*Candida auris* non-candidemia (CANC)[b] (*n*)	*Candida auris* candidemia (CAC)[b] (*n*)	Death in CANC group (*n*)	Death in CAC group (*n*)	*p* value
Diabetes mellitus	11	12	2	9	.012*
Hypertension	10	17	3	12	.056
Central venous catheter	19	27	3	18	.0009*
Intensive care unit (ICU) stay	27	33	6	22	.0008*
Broad spectrum antibiotics	26	34	5	22	.0006*
Mechanical ventilation	22	24	5	18	.0009*
Steroid therapy	24	27	5	20	.0002*
Urinary catheter	17	19	3	13	.0031*
Co-infections along with *C. auris*	13	20	5	15	.067
Previous antifungal therapy	12	7	0	4	.009*

Note: The values in the table are expressed in numbers (*n*). '*n*' denotes the total number of patients. * '*p*' values <.05 were considered significant.

Abbreviations: CAC, *Candida auris* candidemia; CANC, *Candida auris* non-candidemia/colonised.

[a]Underlying disease and mortality association was statistically analysed for diabetes mellitus and hypertension alone. The number of cases for in other underlying diseases were less (refer Table 1), hence no statistical analysis was performed.

[b]The data for underlying diseases and iatrogenic risk factors of CANC and CAC cases were extracted from 10 studies.[13,14,16,22–28]

the equipment or by the healthcare providers. However, Chowdhary et al.[23] proposed that *C. auris* infection in COVID-19 patients may not be transmitted by healthcare personnel because of personal protective equipment (PPE). Further, the authors cautioned that improper use of PPE may lead to contamination and disease transmission.[23] A study from Brazil documented the source of *C. auris*

TABLE 4 Antifungals minimum inhibitory concertation (MICs) for *Candida auris* isolates from COVID-19 patients

Antifungals	No. of isolates	MICs in Range (mg/L)	Geometric Mean	MIC_{50}	MIC_{90}	No. of *C. auris* isolates with MICs (mg/L)													
						0.015	0.03	0.06	0.125	0.25	0.5	0.75	1	2	4	8	16	32	64	128	256	512
Amphotericin B	41	0.125–8	1.29	1	4	0	0	0	1	1	8	5	7	9	9	1	0	0	0	0	0	0
Caspofungin	39	0.125–8	0.597	0.5	2	0	0	0	5	7	8	0	14	3	1	1	0	0	0	0	0	0
Micafungin	27	0.03–8	0.207	0.25	1	0	1	4	8	8	3	0	2	0	0	1	0	0	0	0	0	0
Anidulafungin	38	0.06–8	0.431	0.5	1	0	0	2	5	8	12	0	9	0	1	1	0	0	0	0	0	0
Fluconazole	41	2–512	92.83	256	256	0	0	0	0	0	0	0	0	2	0	2	4	5	4	1	19	4
Voriconazole	41	0.03–8	0.56	1	2	0	3	1	5	6	4	0	10	9	2	1	0	0	0	0	0	0
Isavuconazole	32	0.03–1	0.15	0.125	0.5	0	3	6	11	5	6	0	1	0	0	0	0	0	0	0	0	0
Posaconazole	35	0.015–8	0.095	0.125	0.25	1	9	5	14	3	2	0	0	0	1	0	0	0	0	0	0	0
Itraconazole	23	0.06–16	0.38	0.25	1	0	0	2	2	9	6	0	1	2	0	0	1	0	0	0	0	0
5-Flucytosine	16	0.25–64	6.44	8	64	0	0	0	0	4	0	0	2	0	0	2	1	1	6	0	0	0

Note: The data provided in the table were extracted from 5 studies.[13,14,22–24]

Abbreviations: MIC, minimum inhibitory concentration.

MIC_{50}: MIC at which 50% of the tested isolates are inhibited.

MIC_{90}: MIC at which 90% of the tested isolates are inhibited.

outbreak in the hospital settings; the environmental screening showed *C. auris* contamination from auxiliary digital thermometers (17%), bed rails (15%), and intravenous infusion pumps (11%) and tray tables (11%). The study reported that *C. auris* colonisation of digital thermometer was the significant risk factor associated with *C. auris* colonisation in patients, which correlated with the high isolation rate of *C. auris* from axillae of the patients.[16] Similarly, Eyre et al.[7] reported that skin surface axillary temperature reusable probes were significantly associated with *C. auris* colonisation/infection (86% in the patient group versus 34% in controls). Proper surveillance for *C. auris* colonisation and implementation of infection control practices may stop the spread of *C. auris* infections/colonisation in COVID-19 ICU settings.[7,37]

Candida auris multidrug-resistant isolates have been reported from Asia, the USA, Europe and Africa.[7,38–42] In the present study, *C. auris* isolates were resistant to fluconazole (81%), followed by voriconazole (29.3%), amphotericin B (46.3%), caspofungin (12.8%), anidulafungin (5.1%), micafungin (3.7%) and 5-flucytosine (43.8%). Similarly, antifungal susceptibility testing of *C. auris* isolates from multiple countries reported a large number of isolates are resistant to fluconazole (35%–100%), followed by amphotericin B resistance (8%–61%), echinocandins resistance (0.5%–3%) and voriconazole (14%–90%).[7,38–41] In the present study, multidrug resistance was noted in 53.6% of *C. auris* isolates, similar to the previously reported studies (6%–61%).[40–42]

In the present study, 44 (71%) patients from CANC ($n = 11$, 25%) and CAC ($n = 33$, 75%) group received antifungal therapy. Globally, *C. auris* isolates exhibit a higher susceptible pattern to echinocandins,[7,38–41] making them the drug of choice for *C. auris* infections. Similarly, echinocandins (75%) were the most common drug used in this study. The survival rate for CANC and CAC groups was 77.8% and 35.3%, respectively ($p < .002$). Multiple systematic reviews showed that mortality in *C. auris* cases was at 39% to 47.5%.[4,43] Similar to the present study's findings, Sayeed et al.[10] reported a survival rate of 54% in *C. auris* candidemia cases and 67% in colonised cases. Further, this study showed that iatrogenic risk factors such as prolonged ICU stay, mechanical ventilation, steroid therapy, broad-spectrum antibiotics and central venous catheters were significantly associated with high mortality in CAC patients compared with the CANC group. These findings caution that healthcare personnel should be vigilant while treating severe COVID-19 patients, as they are more vulnerable to *C. auris* infection. Despite the treatment with antifungals, a high mortality rate is seen in *C. auris* infections, making them a global threat.

5 | CONCLUSION

The study highlights the role of hospital-acquired *C. auris* infections in COVID-19 patients. Despite the multiple risk factors possibly favouring the *C. auris* infections in COVID-19 patients, the prevalence of the disease remains unchanged compared with the pre-pandemic. However, one must be cautioned that COVID-19 patients may be

more vulnerable to *C. auris* infections because of the overlapping risk factors. Increased burden of colonised patients with *C. auris* in ICU settings may lead to person-to-person transmission. Hence, proper infection control practices and strict hospital surveillance for screening and isolating *C. auris* colonised patients in the COVID-19 ICUs may prevent the potential outbreaks in hospital settings.

CONFLICT OF INTEREST

The authors declare no competing interest.

AUTHOR CONTRIBUTIONS

HPP conceptualised the idea of this study. HPP, KSV and KCP designed the study. HPP and KSV did primary data extraction for the study and wrote the manuscript. KCP and HPP performed the analysis. The final draft of the manuscript was corrected and proofread by all the authors.

DATA AVAILABILITY STATEMENT

The data generated in the study was provided in the tables and figures of the manuscript.

ORCID

Hariprasath Prakash https://orcid.org/0000-0002-8296-393X

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