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REVIEW ARTICLE

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Global prevalence and subgroup analyses of coronavirus disease (COVID-19) associated *Candida auris* infections (CACa): A systematic review and meta-analysis

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Abstract

Background: Increased hospitalisation rates in the Coronavirus disease 19 (COVID-19) era lead to a new wave of hospital-acquired infections such as emerging multidrug-resistant *Candida auris*. We aimed to evaluate and estimate the global prevalence of coronavirus-associated *C. auris* infection (CACa).

Methods: We searched related databases between December 2019 and April 2022 for studies that reported data about CACa. Meta-analysis was performed using MedCalc software version 20.104 according to the DerSimonian and Laird method applying the random-effects model. We evaluated heterogeneity using the χ^2-based Q statistic (significant for p-value $< .1$) and the I^2 statistic (>75% indicative of 'notable' heterogeneity). Moreover, if possible, an odds ratio (OR) analysis was performed for eligible data.

Results: Our meta-analysis includes ten eligible studies, including 1942 patients hospitalised with COVID-19; 129 were *C. auris* cases. The overall pooled prevalence of CACa was estimated at 5.7%. The mortality rate of CACa was estimated at 67.849%. Hypertension was the most prevalent comorbidity (59.374%), followed by diabetes mellitus (52.898%) and cardiovascular diseases (31.392%). Men with a prevalence rate of 80.012% were 3.27 (OR) times more prone to getting infected by *C. auris*.

Conclusion: We concluded that the prevalence of *C. auris* infections decreased during the COVID-19 pandemic and the prevalence gradient changed from Asia to America. Unfortunately, there are many descriptive studies with duplicate content in the field of epidemiology of *C. auris* infections which are increasing every day. We suggest further non-descriptive studies to accurately establish the cause-and-effect relationships between *C. auris* and COVID-19 infections.

KEYWORDS
Candida auris, coronavirus disease 19 (COVID-19), COVID associated infections, prevalence, risk factors, SARS-CoV-2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infection caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (WHO). Since its emergence in December 2019, many other infections have been associated with this virus.[1] Fungal infections, alongside bacterial and other viral infections, occur as coinfections in COVID-19 patients.[2,3] The well-known COVID-19 associated fungal infections are aspergillosis, mucormycosis and candidiasis.[4,5] *Candida auris* is a multidrug-resistant (MDR) pathogenic yeast that was first described in 2009 after being isolated from the external ear canal of a Japanese patient[6] and followed by otitis media in 15 patients from five hospitals in South Korea.[7] Two years later, *C. auris* was isolated from three bloodstream infections (BSIs) in South Korea, demonstrating its capability to cause invasive infections.[8] Several literature reviews of global culture collections showed that the earliest *C. auris* isolate causing a BSI came from a paediatric surgery patient from South Korea in 1996.[9–11] Nowadays, *C. auris* is a global concern that accounts for nosocomial outbreaks, invasive infections and fungaemia, predominantly in intensive care units (ICUs) across at least 50 countries on six continents.[12–16] The most common risk factors for *C. auris* infections were diabetes mellitus (DM), the extreme age, neutropenia, ICU hospitalisation, pulmonary diseases (PD), cardiovascular diseases (CVSD), kidney diseases (KD), medical devices interventions (MDI), such as catheters and mechanical ventilation (MV), long-time use of broad-spectrum antibiotics and antifungals and immunosuppressive therapy.[17–19]

The U.S Centers for Disease Control and Prevention (CDC) announced *C. auris* in a clinical alert to health care facilities in June 2016.[20] The concerns about this pathogenic fungus grew to the point that in 2019 CDC listed *C. auris* as the first fungus among urgent antimicrobial resistance threats (CDC). According to the geographic origin, *C. auris* can be separated into five Clades: South Asian (Clade I), East Asian (Clade II), South African (Clade III), South American (Clade IV) and Iranian (Clade V).[21,22] The intraclade isolates genetically have the same identity, but interclade strains differ by tens of thousands of single nucleotide polymorphisms (SNP)s.[12,23–25] Reports of *C. auris*-associated outbreaks in the pre- and post-COVID eras are updated daily. Schelenz et al. reported the first outbreak of *C. auris* in a European hospital in London.[26] This outbreak in the U.K involved 72 patients in a specialised cardiothoracic London hospital between April 2015 and November 2016.[27] Moreover, outbreaks in Pakistan,[28] India,[29,30] South Africa[31] and Venezuela[32] were recorded.

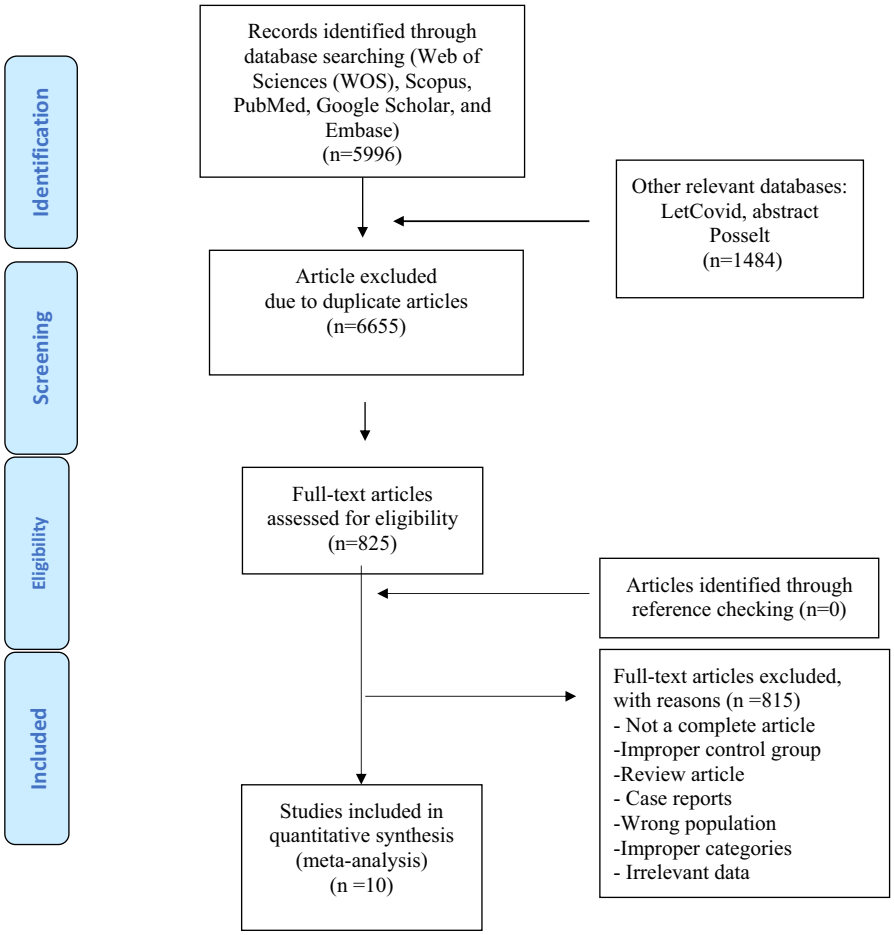
Therefore, concerns about outbreaks of nosocomial infections are so serious that the need to intensify infection control and management policies is becoming urgent. With this perspective, and due to the COVID-19 pandemic and vulnerable ICU patients being the target population for *C. auris* infections, we designed this review to provide accurate statistics on this superinfection. The results of our analysis will be suitable for researchers worldwide to develop preventative policies for infection control.

2 | METHODS

2.1 | Search strategy and selection criteria

The protocol is registered at PROSPERO (Register number: CRD42022289892) (Supplement 1 in Data S1). The present study is conducted and reported according to PRISMA 2020 guideline[33] (Supplement 2 in Data S1). We developed a broad search strategy to identify studies that reported CACa (Supplement 3 in Data S1). In our systematic review, the search terms 'Coronavirus disease', 'COVID-1,9', 'SARS-CoV-2 infection', '*Candida auris*', 'Coinfection' and related terms and words for relevant studies published in PubMed, Web of Science, Scopus, Google Scholar, LitCovid and ProQuest between December 2019 and April 2022 were used (Figure 1). No linguistic or geographical limits were applied. We hand-searched bibliographies of all recovered articles for potentially eligible studies and contacted corresponding authors for published or unpublished data if needed. December 2019 was chosen as the initiation time because it was the initiation date of the COVID-19 infection. Inclusion criteria were as follows: patients with SARS-CoV-2 and *C. auris* infection, all types of studies encompassing data about patients with SARS-CoV-2 and *C. auris* infected simultaneously, including clinical trials, retrospective, prospective and cohort studies, grey literature including conference reports. Exclusion criteria were as follows: patients with SARS-CoV-2 and without *C. auris* infection or patients who have other fungal infections than *C. auris* (e.g. *C. albicans* infections or mucormycosis or aspergillosis), all review type

FIGURE 1 The PRISMA flowchart of the study



studies (e.g. narrative, critical, systematic and meta-analysis and mini-reviews) case reports and case series, all studies including letters to the editor, and editorials, without patient data. Titles and abstracts of references were screened, and the full texts of potentially relevant articles were independently assessed using a standardised score sheet. Studies assessing a clearly defined population of CACa in any clinical setting were included if they had specific diagnostic criteria for *C. auris*. These were predefined using clinical case definitions (based on CDC criteria) or confirmation with laboratory testing using molecular assays, such as sequencing and matrix-assisted laser desorption-ionisation time of flight mass spectrometry (MALDI-TOF MS).

2.2 | Data extraction

Authors independently extracted data and compared it for consistency after data extraction. Discussion and consensus resolved disagreements on final inclusions. The critical variable was the proportion of *C. auris* coinfection among COVID-19 patients. Our denominator was defined as the population of patients who had positive real-time PCR test results for the SARS-CoV-2 virus. Prevalence was defined as the number of *C. auris* cases[34–38] among patients with established SARS-CoV-2 who were inpatients in a hospital or clinic captured by included studies. The following information was captured where available; underlying risk factors, antifungal drug resistance status of *C. auris* isolates (if available), site of isolation of *C. auris* (including clinical sites and medical device intervention) (if available), age and gender of target patients, methods of *C. auris* diagnosis, geographical Clade(s) of *C. auris* isolates (if available) and the health status of patients (death or survival).

2.3 | Risk of bias (quality) assessment

This research involved studies concerning a minimum of three participants to minimise the small-study effect. Authors independently assessed the quality according to the Hoy et al. checklist as previously described Suppl(Supplements 4–13 in Data S1). This checklist explored the various dimensions of empirical proof and methodological assumptions. If required, a consensus was voted by other co-authors to settle the disputes between the investigators. Moreover, the regression-based Egger test and Begg's test for small-study effects will apply to analyse publication bias for our search.

2.4 | Data analysis

Meta-analysis was performed according to the DerSimonian and Laird method applying the random-effects model in case

TABLE 1 Comprehensive and demographic data of the included studies

First author DOP Country Design Reference	Participants						
	COVID-19+	*C. auris* +	Gender	Age	Comorbidities	Medical devise Interventions	Isolation Sites
• Rodriguez et al. • 8 OCT 2020 • Colombia • Multi center observational 44	20	• 6 (30%) • 20 Fungemia Infected	• Men: 13 (65%) • Women: 7 (35%)	63 (1–86)	• HTN: 11 (55%) • DM: 6 (30%) • CKD: 5 (25%) • Cancer: 2 (10%)	• CVC: 19 (95%) • BC: 19 (95%) • MV: 19 (95%) • HMD: 10 (50%) • PBT: 10 (50%)	ND
• Chawdhary et al. • Nov 2020 • India • Single-center observational 51	596	• 10 (1.68%) *C. auris* • 15 Candidemia	☐ In 10 *C. auris* cases: • Men: 7/10 (70%) • Women: 3/10 (30%)	☐ In 10 *C. auris* cases: • 67.1 (25–86) • Eight were > 60	• CLD: 3/10 (30%) • AKD: 1/10 (10%) • HTN: 7/10 (70%) • DM: 6/10 (60%) • HPR: 2/10 (20%) • CKD: 2/10 (20%) • IHD: 2/10 (20%) • Asthma: 2/10 (20%) • COPD: 1/10 (10%)	• MV: 420/596 (70.47%) and 5/10 (50%) • CVC: 15/15 (100%) • UTC: 15/15 (100%)	• Blood: 10/10 (100%) • Urine: 2/10 (20%)
• Magnasco et al. • 3 Jan 2021 • Italy • Single center observational 46	118	• 6 (5.1%) *C. auris* • 6 Candidemia	• Men: 88 (84.6%) • Women: 30 (25.4%) • All *C. auris* patients were Men 6/6 (100%)	• In all patient: 71 • In *C. auris* patient: 62.8 (100% were > 50)	• HTN: 6/6 (100%) • DM: 2/6 (33.3%) • HPR: 2/6 (33.3%) • CAD: 2/6 (33.3%) • COPD: 1/6 (16.7%) • Obesity: 1/6 (16.7%) • LT: 1/6 (16.7%) • Epilepsy: 1/6 (16.7%) • Asthma: 1/6 (16.7%)	ND	• BAL: 2/6 (33.3%) • Blood: 4/6 (66.7%) • Surveillance swabs: 3/6 (50%)
• Prestel et al. • 15 Jan 2021 • USA • Single-center observational 42	67	☐ **Coinfection**: 6/67 (8.95%) ☐ **Colonisation**: 35/67 (52%)	• Men: 21/35 (60%) • Women: 14/35 (40%)	69 (38–101)	Available medical records (*N*: 20) • DM (12/20: 60%) • CW (4/20: 20%) • Cancer (3/20: 15%) • CKD (3/20: 15%) • CPD (1/20: 5%) • Cardiac disease (1/20: 5%) • No underlying conditions (4/20: 20%)	• CVC: 16/20 (80%) • UT: 11/20 (55%) • MV: 11/20 (55%) • Nasogastric/ Gastric tube: 11/20 (55%)	• Body swabs • Clinical cultures
• Almeida et al. • 19 May 2021 • Brazil • Cross-sectional. Observational 53	47	• 3/47 (6.38%) *C. auris* candidemia • 10/47 (21.27%) *C. auris* colonisation (2.12%)	• Men: 1/3 (33.3%) • Women: 2/3 (66.6%)	In *C. auris* candidemia (3/47): 70	• DM: 3/3 (100%) • CKD: 2/3 (66.6%) • HTN: 1/3 (33.3%) • CVD: 1/3 (33.3%) • Obesity: 1/3 (33.3%) • Dementia: 1/3 (33.3%)	• CVC: 3/3 (100%) • MV: 3/3 (100%)	• Blood: 7/10 (70%) • Axillae swabs: 8/10 (80%) • Groin swabs: 5/10 (50%) • Nostrils swabs: 3/10 (30%) • Ear swabs: 2/10 (20%)

Method of diagnosis	Therapy		Antifungal susceptibility tests	ICU admission	Critical Times (mean number of days)	Mortality	Status of ROBA [Point scored]
	Non-antifungal	Antifungal					
• MALDI-TOF MS (100%)	• β-lactam (100%) • Steroids (100%) • DEX (95%)	In 15 from 20: • FLC (40%) • CFG (25%) • VRC (10%)	ND	20 (100%)	• Blood culture positivity to antifungal therapy: 3.9 • Diagnosis of fungemia to the time of death: 6.1 • Admission to initiation of MV: 3	12 (60%)	Low Risk [3]
• MALDI-TOF MS (100%) • Sequencing: ITS (100%) and D1/D2 (100%)	• Antibiotics: 15/15 (100%) • Steroids: 9/15 (60%)	• MFG: 15/15 (100%) • AmB: 6/15 (40%)	• FLC: 10/10 R (MIC >32 mg/L) • VRC: 3/10 R (MIC >2 mg/L) • AmB: 4/10 R (MIC >2 mg/L) • FC: 6/10 R (MIC >32 mg/L) • Multi-azole R (FLC + VRC): 3/10 • Multidrug R: 7/10 • ECH: 10/10 S	596 (100%)	• Hospitalisation days: 20–60 • Admission to development of *C. auris* infection: 10–42	• 8/15 (53%) • 6/10 (60%)	Low Risk [3]
WGS	• Antibiotics: 6/6 (100%) • Steroids: 6/6 (100%)	• CFG: 1/6 (16.7%) • AMB: 1/6 (16.7%)	ND	118 (100%)	• Median ICU stay was 17 days (IQR 8–27 days) • Median time from admission to the first detection of 38 (IQR 26–41)	50 (42.4%)	Moderate Risk [6]
ND	ND	ND	ND	67 (100%)	ND	8/20 (40%)	Moderate Risk [4]
• Vitek-2 • MALDI-TOF/MS • Sequencing: ITS-rDNA • Microsatellite typing • [All isolates belonged to South Asian Clade I]	ND	ANF: 3/3 (100%)	• FLC: 3/3 S (MIC: 4 mg/L) • AmB: 3/3 S (MIC: 1 mg/L) ANF: 3/3 S (MIC: 0.03–0.06 mg/L)	100%	• Hospitalisation before fungemia: 8, 11, 34 •	• 3/3 (100%) • 1 case attributed to fungemia	Low Risk [3]

TABLE 1 (Continued)

First author DOP Country Design Reference	Participants						
	COVID-19+	*C. auris* +	Gender	Age	Comorbidities	Medical devise Interventions	Isolation Sites
• Senok et al. • 21 June 2021 • UAE • Retrospective-cohort observational 48	392	1 coinfection	• Men: 330/390 (84.2%) • Women: 62 (15.8%)	49.3 ± 12.5	• DM: 129/392 (33%) • HTN: 95/392 (24.2%) • Asthma: 18/392 (4.6%) • CD: 18/392 (4.6%) • CKD: 16/392 (4.1%) • Neurological diseases: 9/392 (2.3%) • Cancer: 7/392 (1.8%) • CPD: 5/392 (1.3%)	MV: 201/392 (51.3%)	ND
• Rajni et al. • 7 Sep 2021 • India • Case control 49	103	• 14 *C. auris* • 33 Candidemia	☐ **In candidemia (*n*: 33)** • Men: 24 (73%) • Women: 9 (27%) ☐ **In non-candidemia (*n*: 70)** • Men: 38 (54%) • Women: 32 (44%)	☐ **In candidemia (*n*: 33)** • 66.5 (25–86) ☐ **In non-candidemia (*n*: 70)** • 56 (IQR 27–82)	☐ **In candidemia (*n*: 33)** • HTN: 21 (64%) • DM: 19 (57.5%) • CPD: 5 (15%) • CKD: 3 (9%) • CLD: 5 (15%) • Cancer: 1 (3%) ☐ **In non-candidemia (*n*: 70)** • HTN: 14 (20%) • DM: 7 (10%) • CPD: 3 (4%) • CKD: 2 (3%) • CLD: 2 (3%) • Cancer: 1 (1%)	☐ **In candidemia (*n*: 33)** • CVC: 23 (70%) • UTC: 14 (27%) • MV: 21 (64%) • HMD: 3 (9%) ☐ **In non-candidemia (*n*: 70)** • CVC: 23 (33%) • UTC: 14 (20%) • MV: 24 (33%) • HMD: 2 (3%)	• Blood: 33/33 • Urine: (20/33)

Method of diagnosis	Therapy		Antifungal susceptibility tests	ICU admission	Critical Times (mean number of days)	Mortality	Status of ROBA [Point scored]
	Non-antifungal	Antifungal					
ND	• Lopinavir–ritonavir: 153 (39.03%) • Favipiravir 111 (28.3%) • HCQ: 68 (17.3%) • Ceftriaxone 136 (34.7%) • Azithromycin 74 (18.88%) • Piperacillin–tazobactam 41 (10.46%)	ND	In total (n = 392) • AmB: 100% S • CFG: 98% S • FLC 88% S • FC: 100% S • MFG:100% S • VRC: 97% S (not included to our analysis)	219/392 (55.8%)	• Median duration of hospitalisation: 21 (IQR 12–37) • Mean interval between hospitalisation and commencement of antibiotics: 1.2 ± 3.6 • Median interval between admission and first positive-culture report: 15 (IQR 8–25)	130 (33.2%)	High Risk [7]
• MALDI-TOF Sequencing: • ITS-ITS1 • 5.8S-ITS2 • D1/D2	☐ **In candidemia (n: 33)** • BSA: 33 (100%) • Steroids: 23 (70%) • Tocilizumab: 22 (67%) ☐ **In non-candidemia (n: 70)** • BSA: 70 (100%) • Steroids: 46 (66%) • Tocilizumab: 14 (20%)	ND	☐ **In candidemia (n: 33)** • FLC: 100% R (MIC >32 mg/L) [harboured amino acid substitutions Y132F (n = 9) and K143R (n = 5) in ERG11p. • AmB: 3/33 R (MIC ≥2 mg/L) • FC: 10/33 R (MIC ≥32 mg/L). • Multi-azole: 3/33 R	100%	• Duration of hospital stay: ☐ **In candidemia (n: 33)** <20 days: 9 (27.3%) ≥20 days: 24 (72.7%) ☐ **In non-candidemia (n: 70)** <20 days: 64 (91%) ≥20 days: 6 (9%) • Median ICU stay of 24 days in candidemia	☐ **In candidemia (n: 33)** 21 (64%) ☐ **In non-candidemia (n: 70)** 25 (36%)	Low Risk [3]

TABLE 1 (Continued)

First author DOP Country Design Reference	Participants						
	COVID-19+	*C. auris* +	Gender	Age	Comorbidities	Medical devise Interventions	Isolation Sites
• Moin et al. • 8 Oct 2021 • Pakistan • Retrospective cohort 47	26	4 *C. auris* (15%) from 26 Candidemia	☐ **In *C. auris* cases (*n*: 4)** • Men: 4 (100%) ☐ **In non-*C. auris* cases (*n*: 22)** • Men: 17 (77.27%) • Women: 5 (22.7%)	☐ **In *C. auris* cases (*n*: 4)** • 47 (1–77) ☐ **In non-*C. auris* cases (*n*: 22)** • 56.8 (0.8–82)	☐ **In *C. auris* cases (*n*: 4)** • FSNS: ¼ (25%) • VSD: ¼ (25%) • PDAR: ¼ (25%) • Cancer: ¼ (25%)	☐ **In *C. auris* cases (*n*: 4)** • CVC: 100% • MV: 3 (75%) ☐ **In non-*C. auris* cases (*n*: 22)** • CVC: 15 (68%) • MV: 18 (82%)	• Blood: 26 (100%)
• Niyas et al. • Oct 2021 • India • Retrospective 50	209	• 1 *C. auris* (0.47%) • 4 candidemia (1.91%)	Men: 1	70	• HTN: 1/1 • DM: 1/1	CVC: 100%	Blood
• Alfonso-Sanchez et al. • 10 Nov 2021 • Spain • Prospective Observational 45	364	☐ **Coinfection**: • *C. auris* alone: 14 • *C. auris* with other MDR germs: 15 ☐ **Colonisation**: *C. auris* alone: 14 • *C. auris* with other MDR germs: 24	• Men: 247/364 (67.9%) • Women: 117/364 (31.2%)	ND	ND	ND	• Blood • Urine • Nasopharyngeal

Abbreviations: AFST, antifungal susceptibility test; AKD, acute kidney disease; AmB, amphotericin B; ANF, anidulafungin; BAL, bronchoalveolar lavage; BALL, B cell acute lymphoblastic leukaemia; BC, bladder catheter; CAD, coronary artery disease; CD, cardiac diseases; CFG, caspofungin; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; CPD, chronic pulmonary diseases; CVC, central venous catheter; CW, chronic wound; DEX, dexamethasone; DM, diabetes mellitus; DOP, date of publish; ECH, echinocandins; FC, flucytosine; FLC, fluconazole; FSNS, focal segmental nephrotic syndrome; HCQ, Hydroxychloroquine; HMD, haemodialysis; HPR, hypothyroidism; HTN, hypertension; IHD, ischemic heart disease; IQR, interquartile range; LT, liver transplant; MFG, micafungin; MOLDI-TOF MS, matrix-assisted laser desorption/ionisation-time of flight mass spectrometry; MV, mechanical ventilation; ND, not defined; PBT, packed blood cell transfusion; PDAR, patent ductus arteriosus repair; R, status of resistance; ROBA, risk of bias assessment; S, status of susceptible; UTC, urinary tract catheter; VRC, voriconazole; VSD, ventricular septal defect; WGS, whole genome sequencing.

Method of diagnosis	Therapy		Antifungal susceptibility tests	ICU admission	Critical Times (mean number of days)	Mortality	Status of ROBA [Point scored]
	Non-antifungal	Antifungal					
• BDG test • Germ tube • ChromAgar • API • Microscopic examination,	☐ **In *C. auris* cases (*n*: 4)** • Steroids: 3 (75%) • Tocilizumab: 0 • BSA: 4 (100%) • HCQ: 0 • Remdesivir: 1 (25%) ☐ **In non-*C. auris* cases (*n*: 22)** • Steroids: 19 (86%) • Tocilizumab: 10 (45%) • BSA: 22 (100%) • HCQ: 3 (14%) • Remdesivir: 3 (14%)	☐ **In *C. auris* cases (*n*: 4)** • AmB: 4 (100%) • FLC: 3 (75%) • CFG: 1 (25%) • VRC: 3 (75%) ☐ **In non-*C. auris* cases (*n*: 22)** • AmB: 16 (73%) • FLC: 7 (32%) • CFG: 0 • VRC: 9 (41%)	☐ **In *C. auris* cases (*n*: 4)** • CFG: 100% S • FLC: 100% R • AmB: 100% S (MIC <1 ug/ml) • [AFST Method: Disc diffusion]	100%	☐ **In *C. auris* cases (*n*: 4)** • Hospital stay: 13 days • Hospitalisation duration before candidemia: 20 (13–23) • Days of SARS-CoV-2 positivity at the time of admission (Day 0) to hospital: −2.25 (−10–1) ☐ **In non-*C. auris* cases (*n*: 22)** • Hospital stay: 2.7 days • Hospitalisation duration before candidemia: 9 (1–18) • Days of SARS-CoV-2 positivity at the time of admission (Day 0) to hospital: −2 (−40–3)	☐ **In *C. auris* cases (*n*: 4)** • 50% ☐ **In non-*C. auris* cases (*n*: 22)** • 65%	Moderate Risk [4]
ND	• Remdesivir: 1/1 (100%) • Methylprednisolone: 1/1 (100%) • Favipiravir: 1/1 (100%) • Dex: 1/1 (100%) • Polymyxin B: 1/1 (100%) • Tigecycline: 1/1 (100%)	ND (diagnosed postmortem)	• FLC: 1/1 (100%) R • VRC: 1/1 (100%) R • AMB: 1/1 (100%) R • FC: 1/1 (100%) S • CFG: 1/1 (100%) S • MFG: 1/1 (100%) S	100%	• Days of ICU stay: 7 • Day since SARS-CoV-2 positivity: 12	100%	High Risk [8]
• Vitek-2 • MALDI-TOF/MS	ND	ND	ND	100%	• Length of ICU stay: 211/364 (58%) • Median interval between symptoms onset and ICU admission: 8.4 (SD 7.7) days	113/364 (31.04%)	Low Risk [3]

TABLE 2 Pooled prevalence, subgroup, heterogeneity, and publication analyses result with details

				Heterogeneity			Publication bias				
							Egger's test			Begg's test	
Variables & risk factors	Number of study	Number of cases/eligible CACa cases	Prevalence (95%CI)	I^2(%)	95% CI	Significance level (*p*-value)	Intercept	95% CI	Significance level (*p*-value)	Kendall's tau	Significance level (*p*-value)
Total prevalence	10	65	5.696 (2.774–9.578)	88.67	81.26–93.15	<.0001	4.7021	1.53 to 7.87	.0091	0.5556	.0253
Men	5	19/24	80.012 (56.417–95.818)	44.67	0.00–79.70	.1242	0.1236	−8.225 to 8.472	.9654	−0.2000	.6242
Women	5	5/24	19.988 (4.182–43.583)	44.67	0.00–79.70	.1242	−0.1236	−8.473 to 8.225	.9654	0.2000	.6242
Patients > 50 years old	6	30/30	95.846 (87.018–99.824)	0.00	0.00–0.00	.9931	−1.1568	−1.2374 to −1.0763	<.0001	−1.0000	.0048
DM	5	12/24	52.898 (20.584–83.897)	68.55	19.05–87.78	.0127	1.3894	−9.391 to 12.170	.7092	0.2000	.6242
HTN	5	15/24	59.374 (21.505–91.624)	76.60	43.06–90.38	.0019	−1.3566	−13.95 to 11.242	.7545	0.0000	1.0000
KD	5	6/24	25.508 (8.608–47.573)	32.73	0.00–74.45	.2032	0.3341	−7.216 to 7.8841	.8969	0.0000	1.0000
CVSD	5	1/24	31.392 (16.090–49.131)	0.00	0.00–51.15	.8083	0.2634	−3.639 to 4.1664	.8437	0.0000	1.0000
Cancer	5	5/24	6.964 (0.722–18.844)	0.00	0.00–71.36	.6032	1.6137	−2.581 to 5.8084	.3082	0.6000	.1416
PD	5	4/24	21.680 (8.867–38.204)	0.00	0.00–76.80	.4971	−2.0138	−6.358 to 2.3311	.2367	−0.4000	.3272
LD	5	7/24	18.527 (6.758–34.420)	0.00	0.00–69.04	.6394	−1.8672	−5.421 to 1.6875	.1932	−0.4000	.3272
HPR	5	4/24	18.539 (6.766–34.433)	0.00	0.00–70.22	.6216	−1.3707	−5.733 to 2.9918	.3910	−0.2000	.6242
Obesity	5	2/24	10.516 (2.182–24.023)	43.93	0.00–79.82	.4225	1.7964	−3.356 to 6.9488	.3481	0.4000	.3272
CVC	5	24/24	95.734 (85.545–99.932)	0.00	0.00–0.00	.9765	−1.1559	−1.261 to −1.0505	.0001	−1.0000	.0143
UTC	6	24/38	39.545 (1.923–88.256)	91.73	84.76–95.51	<.0001	−8.1182	−17.324 to 1.088	.0706	−0.2000	.5730
MV	5	17/24	71.707 (41.331–93.918)	61.81	0.00–85.62	.0332	−0.4344	−10.455 to 9.586	.8990	0.0000	1.0000
BSI	7	44/44	96.678 (90.074–99.788)	0.00	0.00–0.00	.9943	−1.1302	−1.197 to −1.0632	<.0001	−1.0000	.0016
UTI	5	2/24	10.977 (2.405–24.661)	0.00	0.00–61.02	.7341	−0.9705	−4.996 to 3.0550	.4988	0.2000	.6242
MALDI-TOF MS	5	47/47	97.648 (91.831–99.967)	0.00	0.00–0.00	.9901	−1.0780	−1.109 to −1.0468	<.0001	−1.0000	.0143
Sequencing	3	27/27	97.575 (89.174–99.949)	0.00	0.00–69.25	.8966	−1.0859	−1.233 to −0.9387	.0068	−1.0000	.1172
Mortality	4	12/18	67.849 (46.122–86.136)	7.41	0.00–88.05	.3561	1.8636	−5.534 to 9.2619	.3917	0.3333	.4969

Abbreviations: BSI, bloodstream infections; CACa, COVID-19 associated *Candida auris*; CVC, central venous catheter; CVSD, cardiovascular diseases; DM, diabetic mellitus; HPR, hypothyroidism; HTN, hypertension; KD, kidney disorders; LD, liver diseases; MALDI-TOF MS, matrix-assisted laser desorption-ionisation time of flight mass spectrometry; MV, mechanical ventilation; PD, pulmonary diseases; UTC, urinary tract catheter; UTI, urinary tract infections.

of considerable heterogeneity, defined as $I^2 > 75\%$. We evaluated heterogeneity using the chi-square (χ^2-based Q statistic, significant for p value < .1) and the I^2 statistic. MedCalc software version 20.104 (MedCalc software Ltd, Acacialaan 22 8400 Ostend-Belgium) was used to perform calculations and the meta-analysis.[39] Odds ratio (OR) analysis was performed for related data if their case(s) and control(s) details were available. Point estimates and 95% confidence intervals were derived using prevalence data from included studies for all outcomes. Where standard errors (SE) were not provided, we incorporated confidence intervals into the formula, SE = (upper limit–lower limit)/3.92. Subgroup analysis and meta-regression were used to determine the source of heterogeneity based on certain putative moderator factors, and sensitivity analysis was used to assess the reliability of our pooling results.

3 | RESULTS

Our meta-analysis included ten eligible studies (Table 1) after an electronic search and the removal of duplicate and irrelevant records (Figure 1). The results of the risk of bias assessment were added to Table 1 (Supplement 4–13 in Data S1). In this analysis, 1942 patients were hospitalised with SARS-CoV-2, and *C. auris* was found in 65 patients. One study each was conducted in the U.S,[40] Brazil,[41] Colombia,[42] Spain,[43] Italy,[44] Pakistan[45] and the UAE,[46] and the remaining three studies were conducted in India.[47–49] We reported both percentage and proportion rates. It should be mentioned that proportion is the relation or the equality between two ratios or fractions (out of any given total), while the percentage is a ratio or a fraction whose denominator is always 100 (out of 100).

3.1 | The pooled prevalence of CACa

The percent rates of CACa cases (by country) in 10 eligible studies were as follows: Colombia 30% (6/20),[42] Brazil 6.38% (3/47),[41] U.S 8.95% (6/67),[40] Italy 5.1% (6/118),[44] Spain 3.85% (14/364),[43] India 2.75% (25/908),[47–49] Pakistan 15.38% (4/26)[45] and the UAE 0.25% (1/392)[46] (Table 2). Results of our random-effects model showed that the overall pooled prevalence of CACa was 5.7% (95% CI: 2.774 to 9.578; I^2: 88.67%; p value: <.0001) (Table 2, Supplement 14 in Data S1, and Figures 2 and 3). As shown by funnel plot in Figure 3 and Table 2, there is a negligible publication bias between studies (intercept: 4.7021; 95% CI: 1.53 to 7.87; p value: .0091).

3.2 | Mortality prevalence of CACa cases

The mortality rate in four studies that reported death from CACa cases was estimated as 67.849% (95% CI: 46.122 to 86.136; I^2: 7.41%; p value: .3561) (Supplement 15 in Data S1) (Table 2).

3.3 | Antifungal therapy (AFT) among CACa patients

A total of 29 out of 65 CACa patients received AFT in 5 studies.[45,47–50] The most applied antifungals are as follows: fluconazole (FLC), amphotericin B (AmB), voriconazole (VRC), caspofungin (CFG), micafungin (MFG), anidulafungin (AFG) and isavuconazole (ISA) (Table 1). The status of susceptibility and resistance (according to CDC-tentative MIC breakpoints) of applied antifungals which presented in 5 studies[45,47–50] from 51 isolates

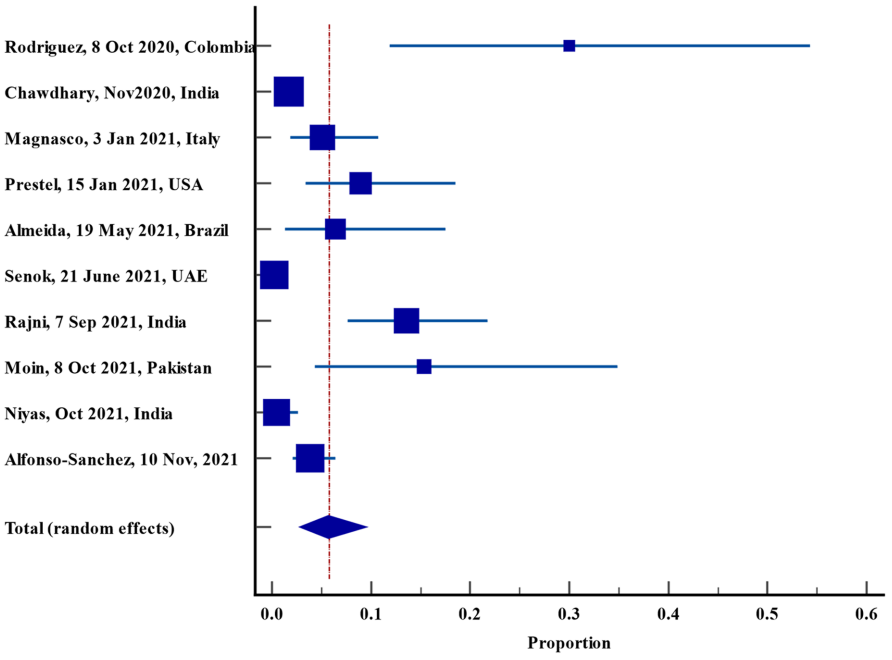


FIGURE 2 Forest plot of the pooled prevalence of CACa

are as follows: FLC: 48R (94.1%); 3S (5.9%), AmB: 8R (15.7%); 43S (84.3%), VRC: 4R (36.4%); 7S (63.6%), MFG: 0R (0.0%); 1S (100%), CFG: 0R (0.00%); 5S (100%), ECHs: 0R (0.00%);10S (100%), 5-flucytosine (FC): 11R (32.4%); 23S (67.6%), multi-azole resistant (MAR): 6R (13.95%); 37S (86.05%) and multi-drug resistant (MDR): 7R (70%); 3S (30%) (Table 3). The prevalence rate of FLC-resistant *C. auris* isolates among CACa patients was estimated 85.062% (95% CI: 51.325 to 99.954; I^2: 81.68%; *p* value: .0002) (Table 3 and Supplement 16 in Data S1). This rate for AmB-resistant isolates was 20.981% (95% CI: 4.634 to 44.931; I^2: 60.79; *p* value: .0372) (Table 3 and Supplement 17 in Data S1). The prevalence rate for FC, VRC, CFG resistant and MAR *C. auris* isolates among CACa patients is reported at Table 3 and Supplement 8–21 in Data S1 respectively.

3.4 | Prevalence and odds ratio of men and women among CACa patients

Five from 10 eligible studies reported patient's gender (*n*: 24), of which 19 were men (79.16%) and 5 were female (20.84%) (Table 2).[44,45,48–50] The pooled prevalence for men was estimated 80.012% (95% CI: 56.417 to 95.818; I^2: 44.67%; *p* value: .1242). The pooled prevalence for women was estimated 19.988% (95%

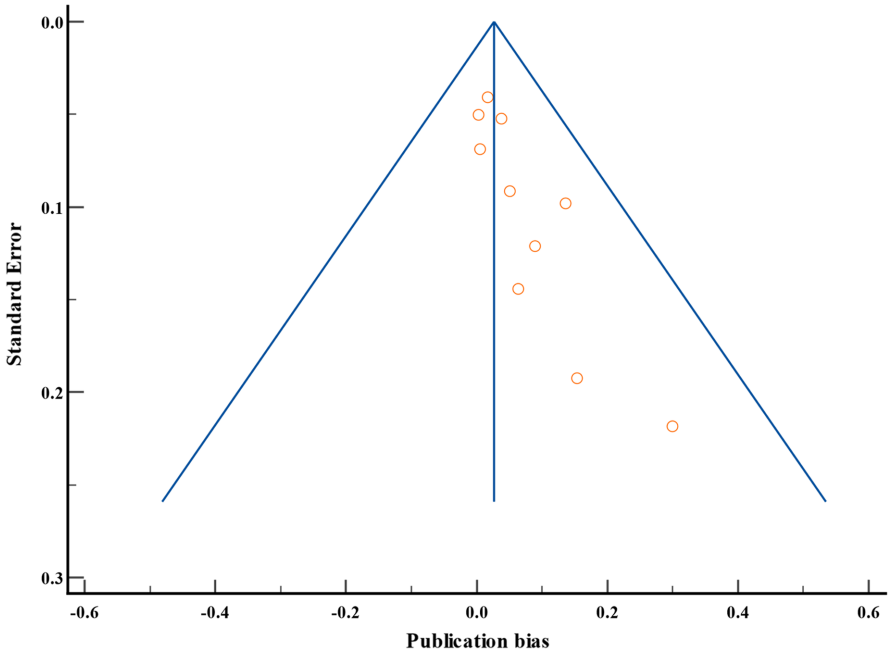


FIGURE 3 Funnel plot of the pooled prevalence of CACa

TABLE 3 The results of subgroup analyses for antifungal resistance status in CACa patients

Antifungals	Number of studies	Number of Isolates	CDC-tentative MIC breakpoints (μg/mL or mg/L)	Resistance percentage (%)	Resistance prevalence (95%CI) (Proportion%)
FLC	5	51	≥32	94.1	85.062 (51.325 to 99.954)
AmB	5	51	≥2	15.7	20.981 (4.634 to 44.931)
VRC	2	11	≥4	36.4	51.463 (6.552 to 94.821)
FC	2	34	ND	32.4	49.834 (5.685 to 94.160)
CFG	2	5	≥4	0.00	7.520 (0.855 to 36.451)
MAR	2	43	ND	13.95	17.675 (2.950 to 41.029)
MFG	1	1	≥2	0.00	–
ECH	1	10	≥2–4 variable	0.00	–
MDR	1	10	ND	70	–

Abbreviations: AmB, amphotericin B; CDC, Centers for Disease Control and Prevention; CFG, caspofungin; ECH, echinocandins; FC, flucytosine; FLC, fluconazole; MAR, multi-azole resistant; MDR, multi-drug resistant; MFG, micafungin; MIC, minimum inhibitory condition; ND, not defined. Notice, Proportion is the relation or the equality between two ratios or fractions (out of any given total), while the percentage is a ratio or a fraction whose denominator is always 100 (out of 100); VRC, voriconazole.

CI: 4.182 to 43.583; I^2: 44.67%; *p* value: .1242) (Table 2 and Supplement 22–23 in Data S1). Moreover, we captured the eligible data for OR analysis of men and women in two studies.[44,45] We resulted that among COVID-19 patients, men have 3.27 times more chance for catching *C. auris* coinfection (OR: 3.27; 95% CI: 0.397 to 26.969; I^2: 0.00%; *p* value: .7555). Women have .306 times fewer risk for catching *C. auris* coinfection (OR: 0.306; 95% CI: 0.0371 to 2.522; I^2: 0.00%; *p* value: .7555) (Table 4 and Supplement 24–25 in Data S1).

3.5 | Subgroup analysis of age of CACa patients

Six of 10 eligible studies reported CACa patients' mean age.[40,44,45,48–50] To facilitate analysis, the data were sorted into two patient groups of mean age: younger than 50 years and older than 50 years. All of CACa patients were ≥ 50 years (Table 1). The pooled prevalence of ≥50 years patients among 30 eligible CACa cases was reported to 95.846% (95%CI:87.018 to 99.824; I^2: 0.00%; *p* value: <.9931) (Table 2 and Supplement 26 in Data S1).

3.6 | Subgroup analysis for ten underlying conditions among CACa patients

As shown in Table 1, five from 10 eligible studies reported 56 episodes of underlying conditions among 24 CACa cases.[44,45,48–50] The most frequent predisposing factors were hypertension (HTN) (15/996; 1.5%) and DM (12/996; 1.2%) followed by CVSD (7/996; 0.7%), KD (6/996; 0.6%), PD (5/996; 0.5%), liver disease (LD) (4/996; 0.4%), hypothyroidism (HPR) (4/996; 0.4%), obesity (2/996; 0.2%) and cancer (1/996; 0.1%). HTN was the most prevalent comorbidity with a prevalence rate of 59.374% (95% CI: 21.505 to 91.624; I^2: 76.6%; *p* value: .0019) (Table 2 and Supplement 27 in Data S1). The prevalence rate of DM was estimated as 52.898% (95% CI: 20.584 to 83.897; I^2: 68.55%; *p* value: .0127) (Table 2 and Supplement 28 in Data S1). Moreover, the prevalence rate of CVSD was estimated as 31.392% (95% CI: 16.090 to 49.131; I^2: 0.00%; *p* value: .8083) (Table 2 and Supplement 29 in Data S1). The results of subgroup analysis of prevalence of KD, PD, and other analysed comorbidities, also the results of publication bias assays were presented in Table 2 and Supplement 30–35 in Data S1.

3.7 | Subgroup analysis for infection sources of *C. auris* isolates among COVID-19 patients

Seven from 10 eligible studies[42,44,45,47–50] reported the origin of clinical isolates (Table 1). BSIs were reported in all 44 eligible CACa cases (100%). The prevalence rate for BSIs was estimated 96.678% (95% CI: 90.074 to 99.788; I^2: 0.00%; *p* value: .9943) (Table 2 and Supplement 36 in Data S1). Moreover, two episodes of urinary tract infections (UTI) occurred among 24 cases (8.3%). The prevalence rate for UTI was estimated as 10.977% (95% CI: 2.405 to 24.661; I^2: 0.00%; *p* value: .7341) (Table 2 and Supplement 37 in Data S1).

3.8 | Prevalence and OR analysis for MDI among CACa patients

Six from 10 studies[42,45,47–50] reported MDI among CACa patients (Table 1). Moreover, we captured the eligible data for OR analysis of MDI in the target population. Among 24 eligible CACa patients,

Heterogeneity			Publication bias				
			Egger's test			Begg's test	
I^2 (%)	95% CI	Significance level (*p*-value)	Intercept	95% CI	Significance level (*p*-value)	Kendall's tau	Significance level (*p*-value)
81.68	57.57 to 92.09	.0002	−2.9096	−9.158 to 3.34	.2350	−0.8000	.0500
60.79	0.00 to 85.29	.0372	1.3933	−3.611 to 6.39	.4409	0.6000	.1416
56.04	0.00 to 89.39	.1315	2.8586	-	<.0001	1.0000	.3173
61.85	0.00 to 91.18	.1055	2.1993	-	<.0001	1.0000	.3173
0.00	0.00 to 0.00	.7006	1.2380	-	<.0001	1.0000	.3173
59.50	0.00 to 90.49	.1161	4.1923		<.0001	1.0000	.3173
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–

TABLE 4 The results of odds ratio analysis in eligible subgroups

			Heterogeneity			Publication bias				
						Egger's test			Begg's test	
Variables & risk factors	Number of study	Odds ratio (95%CI)	I^2 (%)	95% CI	Significance level (*p*-value)	Intercept	95% CI	Significance level (*p*-value)	Kendall's tau	Significance level (*p*-value)
Men	2	3.270 (0.397 to 26.969)	0.00	0.00–0.00	.7555	−8.0326	–	<.0001	−1.0000	.3173
Women	2	0.306 (0.0371 to 2.522)	0.00	0.00–0.00	.7555	8.0326	–	<.0001	1.0000	.3173
CVC	2	2.635 (0.278 to 25.003)	0.00	0.00–0.00	.6294	−7.5747	–	<.0001	−1.0000	.3173
MV	3	0.510 (0.176 to 1.476)	0.00	0.00–87.38	.7666	1.0314	−2.04 to 4.105	.1467	1.0000	.1172

Abbreviations: CVC, central venous catheter; MV, mechanical ventilation.

TABLE 5 Comparison of the epidemiological factors of *C. auris* infections between the pre-COVID and COVID eras

Variable(s)	COVID (This study)	Pre-COVID	Ref (s)
Pooled prevalence (95% CI)	5.696% (95% CI: 2.774 to 9.578)	SR & MA studies: • Sekyere: [*n*: 742], [India: 32.75%, USA: 31.26%, UK: 13.9% (*p* value: .0355) within 2013–2017 • Chen et al. [*n*: 4733] showed a decrease in case count after 2016	9,55
		Descriptive studies: • The 5th most common cause of ICU-onset candidemia. • Discovered in 19 out of 27 ICUs prevalence of 5.3%. • The 6th most common cause of BSI in the hospital between March 2012 and July 2013.	18
Geographical distribution	Mexico (not included), Colombia, Brazil, USA, China, Germany (not included), Italy, India, Pakistan, UAE, Turkey, Lebanon (not included), Spain	SR & MA studies: • Chen et al.: [*n*:4733] [in 33 countries, aligning in descending order: South Africa, USA, India, Spain, United Kingdom, South Korea, Colombia, Pakistan, Kenya, Kuwait, China, Russia, Venezuela, Japan, Panama, Israel, Oman, Germany, Brazil, Saudi Arabia, Singapore, France, Australia, Malaysia, Netherlands, Belgium, Norway, Switzerland, United Arab Emirates, Canada, Iran, Greece, and Italy]	55
		Descriptive studies: • Six continents and above 50 countries	11,12,17–19

TABLE 5 (Continued)

Variable(s)	COVID (This study)	Pre-COVID	Ref (s)
Geographical Clades	[*n*: 1 study] Clade I	SR & MA studies: • Clade I and III were the most prevalent Clades • Clade I was mainly reported in India, Pakistan, Kuwait, Russia, United States, UK, Germany, Malaysia, Netherlands, Italy, etc. • Clade II was mainly in Japan and South Korea. • Clade III was mainly found in South Africa, the USA, the UK, and China. • Clade IV is mainly distributed in Colombia and Venezuela.	55
		Descriptive studies: • All five Clades were reported	11
Age	• The pooled prevalence for ≥50 years subgroup analysis estimated 95.846% (95% CI: 87.018 to 99.824)	SR & MA studies: • NO data were captured	–
		Descriptive studies: • Patients with EA are more susceptible	12,17,56,57
Gender	• Men: 80.012% (95% CI: 56.417 to 95.818) • Women: 19.988% (95% CI: 4.182 to 43.583) • OR for men: 3.270 (95% CI: 0.397 to 26.969) OR for women: 0.306 (95% CI: 0.0371 to 2.522)	SR & MA studies: • Sekyere: Men: 64.76% (*p* value: .0329)	9
		Descriptive studies: • NO data were captured	–
Underlying & risk factor(s)	• HTN: 59.374% (95% CI: 21.505 to 91.624) • DM: 95.846% (95% CI: 87.018 to 99.824) • CVSD: 31.392% (95% CI: 16.090 to 49.131) • KD: 25.508% (95%CI: 8.608 to 47.573) • PD: 21.680% (95%CI: 8.867 to 38.204) • LD: 18.527% (95%CI: 6.758 to 34.420) • HPR: 18.539% (95%CI: 6.766 to 34.433) • Obesity: 10.516% (95%CI: 2.182 to 24.023) • Cancer: 6.964% (95%CI: 0.722 to 18.844)	SR & MA studies: • Sekyere: DM:7%, BSI: 6.4%, Pneumonia: 5.25%, CKD and kidney transplants: 4.3%, Immunosuppression: 3.9%, ST: 3.5%, CVSCD: 3.23%, CLD: 1.9%, (*p* value < .0001)	9
		Descriptive studies: • EA, DM, recent surgery, IMD (e.g., CVC), Immunosuppression, haemodialysis, neutropenia, CKD, BSA, AFT, diarrhoea, HIV, PN, CB	11,12,17–19,56,57
Mortality	• 67.849% (95%CI: 46.122 to 86.136)	SR & MA studies: • Sekyere: Pooled mortality: 29.75% (*p* value: .0488) • Crude mortality per country: 33.33% (South Africa and Israel) to 100% (*p* value: .1789 • Chen et al.: The overall mortality: 39%. • The overall crude mortality of *C. auris* ranged from 0 to 78% • Pooled crude mortality: 39% (95% CI: 32–47%). • The mortality for BSI: 45% (95% CI: 39–51%) • The mortality for non-BSI: 21% (95% CI: 8–33%) [Negligible publication bias and significant heterogeneity (*p* value: <.05; $I^2 = 72\%$)] • Mortality by region: Europe (20, 95% CI: 4–37%) Asia (44, 95% CI: 38–51%).	9,55
		Descriptive studies: • Crude mortality ranges from 30% to 72%. • Overall mortality in BSI: 59 to 68%, respectively. • CDC announced a 59% mortality rate in 5 countries, while only 28% fatality in the outbreak in Venezuela.	17

(Continues)

TABLE 5 (Continued)

Variable(s)	COVID (This study)	Pre-COVID	Ref (s)
Main Diagnostic method for *C. auris*	• MALDI-TOF MS: 97.648% (95% CI: 91.831 to 99.967) • Sequencing: 97.575% (95% CI: 89.174 to 99.949)	SR & MA studies: • Sekyere: Commonly used methods: PCR (30.38%), Bruker MALDI-TOF MS (14.00%), Vitek 2 YST ID (11.93%), AFLP (11.55%), and WGS (10.04%) (*p* value: .002)	9
		Descriptive studies: • Sequencing: 28S D1/D2 rDNA and 18S ITS regions • PCR: D1/D2 region of the 28S rDNA or the ITS region of rDNA • MALDI-TOF MS • Phenotypic methods	11,18,19,56
AFT	Resistance prevalence: • FLC: 85.062% (95% CI: 51.325 to 99.954) • AmB: 20.981% (95% CI: 4.634 to 44.931) • VRC: 51.463% (95% CI: 6.552 to 94.821) • FC: 49.834% (95% CI: 5.685 to 94.160) • CFG: 7.520% (95% CI: 0.855 to 36.451) • MAR: 17.675% (95% CI: 2.950 to 41.029)	SR & MA studies: • Sekyere: R to FLC: 44.29%, R to AmB: 15.46%, R to VRC: 12.67%, R to CFG: 3.48% (*p* value: .0059) • Chen et al.: • The pooled R rate for FLC: 91% (95% CI: 88–95%) • The pooled R rate for AmB: 12% (95% CI: 7–17%) • R to CFG: 12.1% (*n*/*N* = 101/838) in Indian isolates: 23.6% (*n*/*N* = 100/424) • R to MFG: 0.8% (*n*/*N* = 8/927) • R to ANF: 1.1% (*n*/*N* = 9/840)	9,55
		Descriptive studies: • Elevated azole and CFG MICs. • R to FLC: >60–80%, R to AmB: 10–30%, R to ECH: 10%. • Raised MICs to FC. • R to polyenes: (50%), R to ECH: (5%–10%), simultaneous R to two classes of antifungals (azoles and polyenes) • R to FLC: 90% (MICs 32–64 mg/L), R to AmB: 8% (2 mg/L), R to 15% VRC (>1 mg/L), R to ECH: 2.5% (16 mg/L)	12,17–19
Clinical sources of *C. auris* isolates (Clinical manifestations)	• BSI: 96.678% (95% CI: 90.074 to 99.788) UTI: 10.977% (95% CI: 2.405 to 24.661)	SR & MA studies: • Sekyere: blood (67.48%) (*p* value < .0001) • Chen et al.: Pooled rate of the frequency of BSI 32% (95% CI: 21–42%; I^2: 98.7%; *p* value: .00) (varied depending on the Clades) • Clade I and Clade IV have a high percentage of BSI compared to Clade II and Clade III • Clade II: ear discharge as the main specimen type	9,55
		Descriptive studies: • Urine, bile, blood, wounds, the nares, the axilla, the skin, the rectum. • Rarely: gut, oral, oesophageal mucosa, mucocutaneous swabs	11,56,58
MDI	• CVC: 95.734% (95% CI: 85.545 to 99.932) OR for CVC: 2.635 (95% CI: 0.278 to 25.003) • MV: 71.707% (95% CI: 41.331 to 93.918) OR for MV: 0.510 (95% CI: 0.176 to 1.476) • UTC: 39.545% (95% CI: 1.923 to 88.256)	SR & MA studies and Descriptive studies: • NO data were captured	–

Abbreviations: AFLP, amplified fragment length polymorphism; AFT, antifungal drugs; AmB, amphotericin B; ANF, anidulafungin; BSA, broad-spectrum antibiotic; BSI, bloodstream infections; CFG, caspofungin; COM, chronic otitis media; CVC, central venous catheter; CVSD, cardiovascular diseases; DM, diabetic mellitus; ECH, echinocandins; FC, flucytosine; FLC, fluconazole; HPR, hypothyroidism; HTN, hypertension; KD, kidney disorders; LD, liver diseases; MALDI-TOF MS, matrix-assisted laser desorption-ionisation time of flight mass spectrometry; MAR, multi-azole resistant; MDI, medical device intervention; MFG, micafungin; MV, mechanical ventilation; OR, odds ratio; PD, pulmonary diseases; SR&MA, systematic review and meta-analysis; ST, solid tumour; UAE, United Arab Emirates; UK, United Kingdom; USA, United States of America; UTC, urinary tract catheter; UTI, urinary tract infections; VRC, voriconazole.

all were positive for the use of central venous catheters (CVC) interventions during infection control (24/24; 100%) (Table 1). Prevalence rate for CDC was estimated 95.734% (95% CI: 85.545 to 99.932; I^2: 0.00%; *p* value: .9765) (Table 2 and Supplement 38 in Data S1). OR analysis in two studies[42,45] indicated that COVID patients with CVC had 2.635 times more chance of catching *C. auris* coinfection (OR: 2.635; 95% CI: 0.278 to 25.003; I^2: 0.00%; *p* value: .6294) (Table 4 and Supplement 39 in Data S1). About 17 out of 24 CACa cases were positive for the use of MV during their therapeutic processes (70.8%) (Table 1). Prevalence rate for MV was estimated 71.7% (95% CI: 41.331 to 93.918; I^2: 68.81%; *p* value: .0332) (Table 2 and Supplement 40 in Data S1). OR analysis in three studies[42,45,49] indicated that COVID patients with MV had 0.51 times fewer risk for catching *C. auris* coinfection (OR: 0.510; 95% CI: 0.176 to 1.476; I^2: 0.00%; *p* value: .7666) (Table 4 and Supplement 41 in Data S1). Moreover, 24 from 38 (63.16%) of CACa cases were reported to use of urinary tract catheter (UTC) (Table 1). Prevalence rate for UTC was estimated 39.545% (95% CI: 1.923 to 88.256; I^2: 91.73%; *p* value: <.0001) (Table 2 and Supplement 42 in Data S1).

3.9 | Subgroup analysis for the method of diagnosis of *C. auris* among CACa population

MALDI-TOF MS successfully detected all 47 eligible *C. auris* cases (not isolates) (100%) in five studies.[42,43,47,49,50] Prevalence rate for use of this diagnostic method was estimated 97.65% (95% CI: 91.831 to 99.967; I^2: 0.00%; *p* value: .9901) (Table 2 and Supplement 42 in Data S1). Moreover, sequencing of ITS rDNA and D1/D2 regions was used to detect 27 *C. auris* in 27 eligible cases (100%) in three eligible studies.[47,49,50] Prevalence rate for use of this diagnostic method was estimated 97.575% (95% CI: 89.174 to 99.949; I^2: 0.00%; *p* value: .8966) (Table 2 and Supplement 44 in Data S1). We found one study reporting geographical Clades of *C. auris* isolates (Clade I).[50]

4 | DISCUSSION

Candida auris is an emerging MDR pathogen becoming a global threat due to its nosocomial spread,[51] especially in the COVID-19 era.[52,53] Our meta-analysis includes ten eligible studies, including 1942 patients hospitalised with COVID-19. Nearly 129 of them were reported as *C. auris* cases. The overall pooled prevalence of CACa was estimated as 5.7%. The mortality rate of CACa was estimated at 67.849%. Hypertension was the most prevalent comorbidity (59.374%), followed by diabetes mellitus 52.898% and cardiovascular diseases (31.392%). The prevalence rate for men's CACa cases was 80.012% and for patients older than 50 years was reported as 95.846%. Moreover, we resulted that men were 3.27 times more prone to getting infected by *C. auris*. BSI was the most prevalent form of CACa (96.678%), and CVC was the most applied medical device during the infection control (prevalence rate: 95.734%). The OR analysis results indicated that COVID patients who applied CVC had 2.635 times more chance of catching *C. auris* coinfection. MALDI-TOF MS and sequencing of ITS and D1/D2 regions were the most prevalent methods to diagnose *C. auris*-positive patients (97.648% and 97.575% respectively). We reached a high heterogenicity rate (I^2: 88.67; *p* value: <.0001) (Table 2). This could be explained by various factors, including different methods/populations included in our analysis and different geographical distribution of *C. auris* and SARS-CoV-2 cases. The subgroup analysis was used to moderate the effect of high heterogeneity. Thus, as shown in Table 2, heterogeneity was reduced in most of our study's subgroup analyzes.

There is a lack of data about the prevalence of *C. auris* infections. We found only two systematic reviews and meta-analyses (SR&MA) in the literature related to the pre-COVID era.[9,54] However, there are several descriptive studies.[11,12,17–19,55–57] Although a recent study published by Indian researchers[58] reported a 14% pooled prevalence rate for CACa cases, it does not seem logical to compare their results with our study for various reasons. One of these reasons is the inclusion of case reports and case series (for instance, Mexico and Lebanon) in their final analysis, despite current guidelines for prevalence and incidence data.[59–63] Case reports and case series studies that report a 100% prevalence rate give false effects on the elevation of pooled prevalence rate, reporting biases and heterogeneity. Nevertheless, analysing these kinds of studies needs to consider specific protocols and guidelines,[63–66] but this was not clarified in the Indian study.

To facilitate the comparison between our findings and the pre-COVID data, Table 5 was designed and added. We reviewed two SR&MA studies[9,54] about the epidemiology of *C. auris* infections in the pre-COVID era. Chen et al.[54] from China analysed the data of 4733 *C. auris* isolates and showed a decrease in case of count after 2016. Moreover, an analysis of Sekyere[9] from Ghana on 742 isolates indicated a 32.75% prevalence rate in India, 31.26% in the USA and 13.9% in the UK, from 2013 to 2017 (*p*-value: .0355) (Table 5). During COVID-19, a study by Garcia-Vidal et al. from Spain[67] reported a prevalence rate of 0.7% (7/989) for IFI among COVID-19 patients. Moreover, a study from the UK[68] reported 12.6% and 14.1% prevalence rates for yeast and aspergillus coinfections among COVID-19 patients respectively. Arastehfar et al.[69] reported that four *C. albicans* (0.2%) and two *C. glabrata* (0.1%) were isolated from 1988 COVID-19 patients in Iran. However, currently, there are no reported cases of CACa in Iran. Compared with their findings, we resulted that the prevalence of *C. auris* infections among the COVID-19 population is lower than in the pre-COVID era (5.7% prevalence rate) (Table 2, Figures 2 and 3, and Supplement 14).

The extent of COVID-associated candidiasis (CAC)s varies by country and region.[69,70] The geographical distribution of *C. auris* in the pre-COVID era was in 33 countries and six continents[54] and was higher in India and USA[9] (without statistical confirmation). While we showed that the occurrence of CACa in North, Central and South America is higher than in other regions, maybe because of higher rates of COVID-19 in these regions. Therefore, we assume that the

COVID-19 outbreak may change the prevalence gradient of *C. auris* infections from Asia to America. However, the small number of initial studies may not generalise to all CACa cases. Moreover, Chen et al. indicated that Clade I and Clade III were the most prevalent Clades (Table 5). We found one study reporting geographical Clades of *C. auris* isolates (Clade I)[50]; comparing them with pre-COVID data does not seem logical due to the low amount of data. Moreover, Sekyere[9] showed that 64.76% of *C. auris* cases were men (*p* value: .0329) (Table 5). Compared with our findings, the COVID-19 pandemic did not affect the susceptibility of men to *C. auris* coinfections (men: 80%, women: 20%). However, we resulted that COVID-19-positive men were 3.27 times more prone to getting infected by *C. auris* (Table 2 and Supplements 22–25 in Data S1).

During the pre-COVID era, Sekyere[9] reported a pooled mortality rate of 29.75% (*p* value: .0488) and crude mortality per country: 33.33% (South Africa and Israel) to 100% (*p* value: .1789) for *C. auris* infections (Table 5). Moreover, Chen et al.[54] reported that the overall mortality rate for *C. auris* infections was 39% and for *C. auris* BSI and non-BSI were 45% (95% CI: 39–51%) and 21% (95% CI: 8–33%) respectively. Moreover, they analysed the mortality by region, resulting in higher rates in Asia 44% (95% CI: 38–51%) than Europe 20% (95% CI: 4–37%). Overall mortality rates of invasive *C. auris* infection ranged from 30% to 59% globally.[23,52] In addition, the in-hospital mortality rate ranged from 30% to 72%[57] (Table 5). In two studies from a Middle Eastern country, Oman, the overall fatality rate in ICU-admitted patients was 52.5%[71] and 53.1.[72] Moreover, Hu et al. reported a 47.5% mortality rate among 476 cases of *C. auris*.[73] Compared with the pre-COVID era, we resulted that the mortality rates in patients with *C. auris* and COVID-19 infections increased with a slight slope (overall mortality rate of 67.85% in our analysis) (Table 2 and Supplement 15 in Data S1).

Sekyere[9] analysed the underlying and risk factors for *C. auris* infection in the pre-COVID era and showed that DM (7%), pneumonia (5.25%), KD (4.3%), immunosuppression (3.9%) and solid tumours (3.5%) were the main among them (Table 5). Moreover, Arastehfar et al.[70] and Roudbary et al.[74] reviewed underlying conditions and the role of the microbiome and immune responses in CAC patients. Compared with our findings, we resulted that the COVID-19 pandemic leads to a shift in underlying risk factors for *C. auris* infections (HTN > DM > CVSD > KD > PD > HPR > LD > cancer). (Table 2 and Supplement 27–35 in Data S1). However, the small number of CACa cases may not generalise to all CACa cases. During the pre-COVID-19 era, two SR&MA studies analysed clinical manifestations and sources of *C. auris* infections.[9,54] Sekyere[9] indicated a 67.48% rate for bloodstream *C. auris* infections (*p* value < .0001). Chen et al.[54] showed that the pooled rate of the frequency of BSI was 32% (95% CI: 21 to 42; I^2: 98.7%; *p* value: .00) (varied depending on the Clades; Clade I and Clade IV high percentage of BSI compared with Clade II and Clade III) (Table 5). Compared to the pre-COVID era, we resulted that the clinical manifestations of *C. auris* infections were changed during the COVID-19 era (BSI: 96.68%, UTI: 10.98%) (Tables 2 and Supplement 36–37 in Data S1). However, the high rate of BSIs may be related to developed diagnostic methods and different sources of clinical isolates.

Before the emergence of drug resistance, azoles were the first line antifungal drug against *C. auris* infections.[52,75,76] It is reported that more than 90% of *C. auris* isolates from all five geographical Clades are FLC-resistant.[23,77] More than 30% and about 10% of the isolates were resistant to AmB and echinocandins (ECH) s respectively.[23,78] Moreover, 30 to 41% (one-third) of isolates are resistant to at least two antifungal drugs, and 4% of isolates are resistant to all clinically available antifungals.[23,78] Due to the low resistance rates, ECHs are the most useful antifungals.[23,78,79] SR&MA studies analysed antifungal resistant patterns in the pre-COVID era.[9,54] Sekyere[9] indicated the resistant rates to FLC: 44.29%, AmB: 15.46%, VRC: 12.67% and CFG: 3.48% (*p* value: .0059). Moreover, Chen et al.[54] analysed the pooled resistant rate for FLC: 91% (95% CI: 88–95%), AmB: 12% (95% CI: 7–17%), CFG: 12.1% (*n*/*N* = 101/838), MFG: 0.8% (*n*/*N* = 8/927) and AFG: 1.1% (*n*/*N* = 9/840) (Table 5). Compared with our findings (FLC: 85%, VRC: 51%, FC: 40.83%, AmB: 21% and MAR: 17.67%), there were no sensible changes in the resistance patterns during the COVID-19 pandemic (Table 3 and Supplement 16–21 in Data S1). Sekyere[9] indicated that PCR (30.38%), MALDI-TOF MS (14.00%), Vitek-2 (11.93%), AFLP (11.55%) and WGS (10.04%) were the main molecular diagnostic methods of *C. auris* isolates in the pre-COVID era (*p* value: .002) (Table 5). However, we found that MALDI-TOF MS and sequencing of ITS and D1/D2 regions were the most prevalent methods to diagnose *C. auris*-positive patients (97.648% and 97.575% respectively) (Table 2 and Supplement 43–44 in Data S1). However, our work is not without limitations. No publications describing CACa data are available; thus, surveillance data has been hard to collect and publish during the COVID-19 pandemic when researchers and public health are busy. The studies here probably represent a small fraction of CACa and are not representative of all CACa cases.

5 | CONCLUSION

The prevalence of *C. auris* infections among the COVID-19 population is lower than the pre-COVID era. Moreover, the prevalence gradient of *C. auris* infections changed from Asia to the Americas during the COVID-19 era. We concluded that the mortality rates in patients with *C. auris* infections were increased in the COVID-19 era with a slight slope. Our findings show that candidemia is the most common clinical manifestation of CACa and FLC was the most resistant antifungal agent in the pre- and post-COVID-19 eras. Moreover, there were no sensible changes in the antifungal resistance patterns in the pre- and post-COVID eras. Unfortunately, there are many descriptive studies with duplicate content in the field of epidemiology of *C. auris* infections which are increasing every day. We suggest further retrospective, case–control, and prospective studies in this field and avoiding case reports and case series due to their uselessness in meta-analysis. Avoiding the designing and publishing descriptive

studies without adding novel data to the field is recommended. Finally, more precisely systematic review and meta-analysis studies with lower heterogeneity rates are needed to add to the field and accurately establish the cause-and-effect relationships between *C. auris* and COVID-19 infections.

AUTHOR CONTRIBUTIONS

HM, NV, JSH, HB and FS performed initial searches, screened, and selected eligible studies. HM, NV, HK and HB evaluated the risk of bias assessment and quality control of included studies. HM, HK, FA and SN extracted the data. HM, HB and JM analysed and interpreted the data. NV, JSH, HM, JM, HK and HB drafted the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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SUPPORTING INFORMATION

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