Iranian Journal of Microbiology
Volume 14 Number 3 (June 2022) 276-284

REVIEW ARTICLE

Candida auris: outbreak fungal pathogen in COVID-19 pandemic: a systematic review and meta-analysis

Kamran Bagheri Lankarani[1], Maryam Akbari[1*], Reza Tabrizi[2,3], Mohebat Vali[4], Eghbal Sekhavati[1], Seyed Taghi Heydari[1], Hossein Khodadadi[5], Fariba Ahmadizar[6]

[1]Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran
[3]Clinical Research Development Unit of Vali Asr Hospital, Fasa University of Medical Sciences, Fasa, Iran
[4]Department of Epidemiology, Shiraz University of Medical Sciences, Shiraz, Iran
[5]Department of Parasitology and Mycology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[6]Julius Global Health, University Utrecht Medical Center, Utrecht, The Netherlands

Received: October 2021, **Accepted:** March 2022

ABSTRACT

Background and Objectives: *Candida auris (C. auris)* is the first fungal pathogen considered a global health threat. Because, *C. auris* is associated with multidrug resistance and associated diseases such as diabetes, sepsis, lung and kidney disease. This study investigated the prevalence and mortality of *C. auris* infection during Covid-19 pandemic.
Materials and Methods: Databases were searched for peer-reviewed articles published in the English language up to Jan 18, 2022. Heterogeneity across studies was evaluated using Cochrane's Q test and the I2 index. The pooled point prevalences and their corresponding 95% confidence intervals (CIs) were estimated usingthe random-effects model.
Results: In our meta-analysis, 11 eligible articles were included. The total pooled prevalence estimation of *C. auris* infection among COVID-19 patients was 13% (95% CI: 8%, 19%). The estimated pooled mortality rate of *C. auris* infection was 37% (95% CI: 15%, 61%). In terms of specific conditions, the pooled risk of mortality was higher in people with diabetes 65% (95% CI: 0.45%, 83%), in cases with >21 days admission inintensive care unit (ICU) 44% (95% CI: 21%, 0.68%), and after receiving steroids 43% (95% CI: 18%, 69%).
Conclusion: Our study highlights the high prevalence rate of *C. auris* infection, particularly among people with a history of metabolic disorders.

Keywords: *Candida auris* infection; COVID-19; Disease outbreaks; Meta-analysis

INTRODUCTION

Up to one-third of patients with coronavirus infection (COVID-19) may require hospitalization in the intensive care unit (ICU) due to severe respiratory failure (1, 2). However, protective measures applied to patients with COVID-19 are often not primarily intended to prevent cross-transmission of pathogens between hospitalized patients. Even before the current epidemic, the emergence of antimicrobial

*Corresponding author: Maryam Akbari, Ph.D, Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran. Telefax: +98-71-32309615 Email: m.akbari45@yahoo.com

resistance among bacteria and fungi is one of the major threats worldwide (3, 4). Optimizing the antimicrobial prescription may be challenging among COVID-19 patients, especially critical patients, as clinical severity, imaging features, and laboratory parameters make it difficult to distinguish common bacterial infection from the effects of the virus itself. Similarly, measures to limit the prevalence of resistant pathogens may be difficult in hospital settings such as COVID-19 ICUs (5).

Candida auris is one of these pathogens. *Candida auris* was initially discovered as a novel yeast species belonging to the genus *Candida* after being isolated from the ear of a Japanese female patient in 2009 (6). *C. auris* was the first fungal pathogen considered a global health threat. Information on patients infected with this pathogen was reported to local public health authorities (7). *C. aurisis* associated with multidrug resistance and comorbidities such as diabetes, sepsis, lung and kidney diseases (8). This pathogen spreads through person-to-person contact in a hospital setting; thus, it has a different transmission route from other *Candida* species, which are usually a component of the patients' microbiome and are considered as part of the host gastrointestinal flora (9). The virulence factors of *C. auris* are the same as other *Candida* species; however, these species can also escape the innate immunity and form biofilms that are resistant to all antifungal agents (10, 11). The incidence of *C. auris* infection can reach up to 68%, from colonization to invasive disease and candidiasis with high mortality (12). However, it is difficult to detect it by traditional laboratory methods (13). Over the past ten years, more than 35 countries have reported *C. auris* cases, including nine Middle Eastern countries. Based on existing evidence, four major clades appeared spontaneously in different parts of the world, including East Asia, South Asia, Africa, and South America. Later, a potential fifth clade was reported from Iran (14). In the Middle East, the first case was reported in 2014 from Kuwait (15-17), and subsequent cases were reported from Israel (18), Oman (19, 20), Saudi Arabia (21, 22), the United Arab Emirates (23), Iran (14, 24), and Qatar (25).

Given that this fungus can be closely related to COVID-19 disease, especially in hospitalized patients, the study of this fungus's prevalence and mortality in Covid 19 patients can help us to determine a specific guideline to control this disease. Therefore, this systematic review and meta-analysis investigated the prevalence and mortality of *C. auris* infection during the COVID-19 pandemic.

MATERIALS AND METHODS

Search strategy and selection criteria. The searches were performed in PubMed, Embase, Scopus, and Web of Science for peer reviewed-articles published in English upto January18, 2022. The terms including: "COVID-19", "Novel Coronavirus", "Coronavirus Disease 2019", "*Candida auris*", "*C. auris*", "Co-infection", and "Comorbidities" were used. The list of titles and abstracts and the full paper of the selected citations were independently examined by two reviewers (MA and RT). PRISMA flow diagram is presented in Fig. 1. We conducted and reported this study based on PRISMA guidelines.

Inclusion and exclusion criteria. Studies were included if were: (1) among COVID-19 patients with *C. auris* in all ages and with confirmed severe acute (we defined severe cases as intensive care unit (ICU) admission or requiring mechanical ventilation) respiratory syndrome, and 2) observational designs such as case series, cross-sectional or prospective and retrospective cohorts. We excluded systematic reviews, case reports, non-English articles, studies concerning genetically related *C. auris* or cell biology, and studies investigating drug resistance and management.

Data extraction. The data from the included studies were extracted by two reviewers (MA and MV) independently. Also, a third reviewer (RT) was used to solve any arisen argument. The details of each study were collected, including first author, publication year, study location, study design, number of cases with severe or critical COVID-19, number of cases with *C. auris*, number of deaths with *C. auris*, basic characteristics of participants (includes age, gender, risk factors), steroid intake, intensive care admission time (ICU) length of stay, and the outcome at the last follow-up.

Quality assessment. The quality of the methods used in each article was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal guidelines for the case series by three independent reviewers (MA, RT, and KBL) (26, 27). This tool evaluated studies

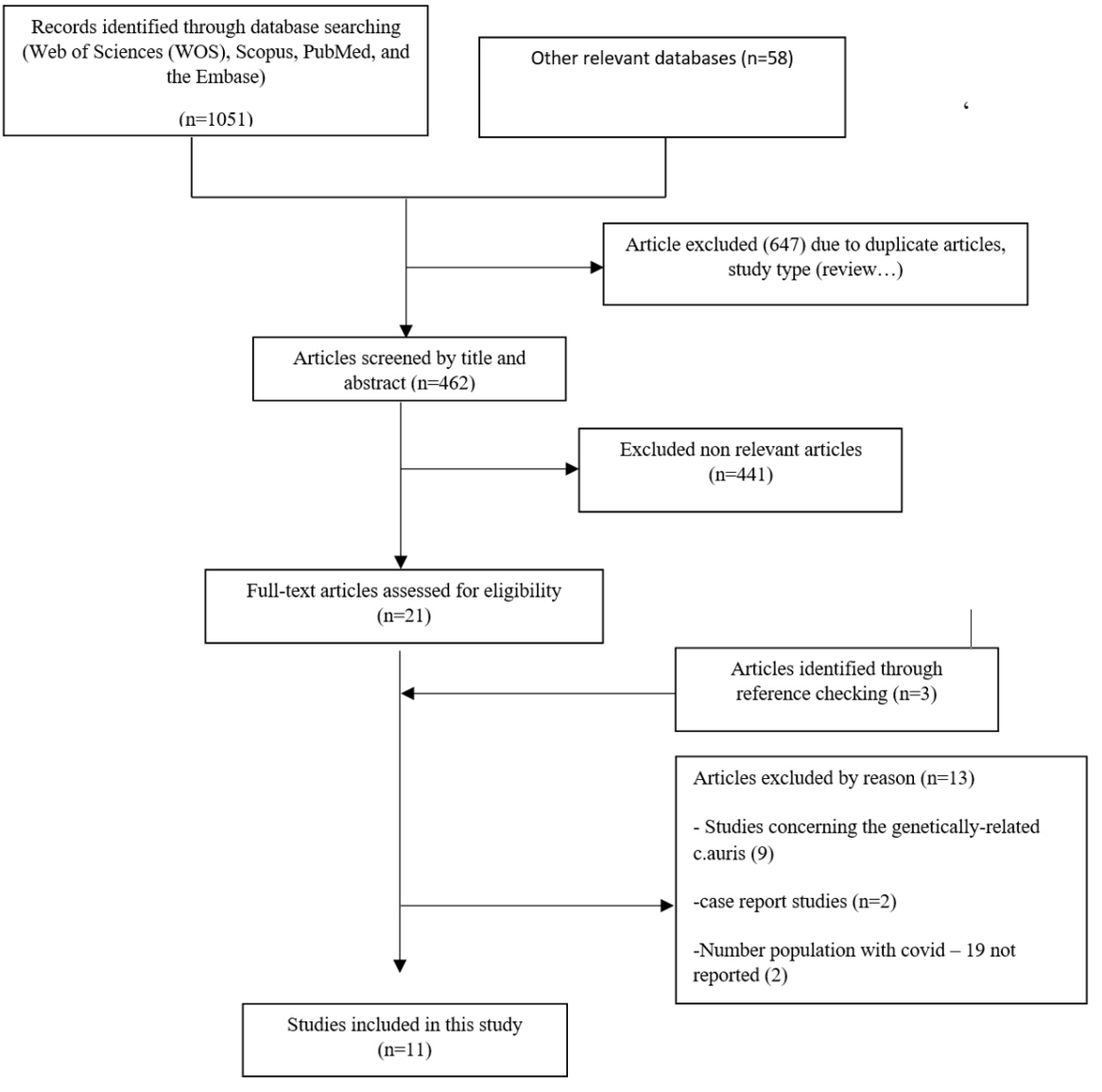

Fig. 1. Flowchart of study identification and selection process

according to dimensions, including a clear presentation of inclusion/exclusion criteria and patient/clinical information, reliable testing for disease confirmation, the inclusion of an appropriate sample population, and appropriate statistical testing. Supplementary Table 1 shows more details of quality assessment for each included study.

Statistical analysis. All statistical analyses were performed using STATA version 12.0 (Stata Corp., College Station, TX). Heterogeneity across studies was evaluated using Cochrane's Q test and the I^2 index. I^2> 50% with a P <0.1 for Cochrane's Q test showed the presence of heterogeneity. The pooled point prevalences and their corresponding 95% confidence intervals (CIs) were considered to describe the prevalence of *C. auris* infection in COVID-19 patients. The standard error of each point prevalence was estimated based on the binomial distribution formula. And also, the mortality rate in patients with *C. auris* across included studies was combined using the metaprop function with Freeman-Tukey double arcsine transformation method due to deaths having 0 or 100 percent. The random-effects model was utilized for pooling all of the point prevalences in the current meta-analysis. We performed additional analyses, including subgroup analysis to assess the source of heterogeneity based on some potential moderator vari-

Table 1. the main characteristic of included studies

Author (s)	Year publication	Country	Study design	Total Cases with covid-19	Total Cases with *C. auris*	Age mean (Median)	Sex	Risk factors	Steroid Intake	Days in ICU (median)	outcome at the Last Follow-Up	Diabetics	Use of antibiotics
Villanueva-Lozano et al. (34)	2021	Mexico	cross sectional	60	12	54.9 (54.5)	83% male	HBP, DM, obesity, asthma, CAD, AKI, smoking, hypothyroidism, VHD, and antibiotic use	Yes	24.5	9 Died / 3 Alive	Yes	Yes
Gaitan (31)*	2020	Spain	Cross-sectional	61	1	N/A	N/A	Mechanical ventilation, parenteral nutrition, broad-spectrum, anti-bacterial treatment, indwelling central venous or bladder catheters, older age, comorbidities, lymphopenia, and corticosteroids	Yes	13	0 Died / 1 Alive	N/A	Yes
Puchades (31)*	2020	Spain	Cross sectional	62	4	N/A	N/A	mechanical ventilation, parenteral nutrition, broad-spectrum, anti-bacterial treatment, indwelling central venous or bladder catheters, older age, comorbidities, lymphopenia, and corticosteroids	Yes	36.4	0 Died / 4 Alive	N/A	Yes
Chowdhary et al. (29)	2020	India	Retrospective cohort	569	10	67 (70)	70% male	CLD with grade II, encephalopathy, AKD, antibiotic use, DM, hypothyroidism, on dialysis for CKD stage 5, steroid therapy, CVC, and UC, asthma, and IHD	Yes	21	6 Died / 4 Alive	Yes	Yes
K. Price et al. (36)	2021	California	Retrospective cohort	113	6	63.4 (65)	N/A	Coronary artery disease, stroke, chronic respiratory fracture, tracheostomy and ventilator dependence, gastrostomy tube dependence, urinary incontinence, multiple ulcers, heart failure, atrial fibrillation, hypertension, hyperlipidemia, tracheostomy, and gastrostomy	N/A	N/A	N/A	N/A	No
Zuo et al. (35)	2020	Hong Kong	case series	30	5	52.4 (63)	40% male	Anti-bacterial treatment, hypertension, renal impairment, and hyperlipidemia	N/A	11	0 Died / 5 Alive	N/A	Yes
Prestel et al. (32)	2021	Florida	case series	35	6	69	N/A	Diabetes, chronic wound/wound care, malignancy, chronic kidney disease, chronic lung disease, and cardiac disease	N/A	N/A	N/A	Yes	No
Rodríguez et al. (33)	2021	Colombia	case series	20	6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Unknown
Di Pilato et al. (30)	2021	Italy	case series	22	10			Antifungal drugs	N/A	70	5 Died / 5 Alive	N/A	Yes
Magnasco et al. (30)	2021	Italy	Retrospective cohort	118	6	62.8 (63)	100% male	Type 2 diabetes mellitus, obesity, CAD, hypertension, and asthma	Yes	32	3 Died / 3 Alive	Yes	Yes
Allaw et al. (28)	2021	Lebanon	case series	26	14	72.1 (74.5)	57% male	Cutaneous T cell, lymphoma, small bowel obstruction, brain abscess, cancer, COPD, ARDS, and acute respiratory distress syndrome	Yes	52.5	5 Died / 9 Alive	N/A	Yes

*Authors have communicated in different hospitals in the same article.
N/A: not Applicable
ICU: Intensive care units
HBP: High blood pressure
DM: Diabetes mellitus
CAD: Coronary Artery Disease
AKI: Acute Kidney Injury
VHD: Valvular Heart Disease
CLD :Chronic Lung Disease
AKD: Acute Kidney Disease
CKD :Chronic Kidney Disease
UC: Urine Culture
IHD: ischemic heart disease
COPD: Chronic Obstructive Pulmonary Disease
ARDS: Adult Respiratory Distress Syndrome

ables and sensitivity analysis to indicate the reliability of our pooling findings.

RESULTS

After electronic searching and removing duplicate and irrelevant recodes, 11 eligible articles (28-36) were included in our meta-analysis. We included Pemán et al. (2020) study (31) as two articles because the Puchades and Gaitan (2020) had reported separately different data on this study. The total population of patients admitted as COVID-19 was 1,116 in these studies. Of these, 80 patients had *C. auris* infection. Four out of 11 articles were carried out in the USA (32-34, 36), two were in Spain (studies by Puchades and Gaitan (2020) (31) and Italy (30), and the remaining three studies were performed in Lebanon, China (35), and India (29). The main basic characteristics of studies were summarized in Table 1.

The pooled prevalence of *C. auris* infectionin COVID-19 patients. The total prevalence of *C. auris* infection in COVID-19 patients in studies entering into our meta-analysis varied from 1.64% in Rodríguez et al. (2020), study (33) to 53.85% in Puchades (2020) study (31). The total pooled prevalence of *C. auris* infection among COVID-19 patients was 13% (95% CI: 8%, 19%) by using the random-effects model (Fig. 2A). Due to the presence of heterogeneity across included studies (I^2 = 87.8%, P <0.01), we conducted subgroup analysis to assess the source of heterogeneity based on length of stay at ICU (<21 days vs. >21 days vs. Unknown) and study designs (case-series vs. cross-sectional vs. cohort). The pooled estimate showed that the prevalence of *C. auris* infection was more common among patients with > 21 days at ICU admission [23% (95% CI: 10%, 37%)] compared to patients with < 21 days [3% (95% CI: 1%, 8%)], and unknown group [15% (95% CI: 1%, 29%)]. In terms of specific study designs, the pooled meta-analysis for case-series was estimated to be 32% (95% CI: 17%, 46%), for cross-sectional 8% (95% CI: 1%, 18%), and for cohort 3% (95% CI: 1%, 6%).

In sensitivity analysis to indicate the reliability of our pooling results using user-specified I^2 (25%), we found the total pooled estimation of *C. auris* infection prevalence among COVID-19 patients was changed from 13% (95% CI: 8%, 19%) to 6% (95% CI: 4%, 6%).

Pooled mortality rate of *C. auris* infection in COVID-19 patients. In 8 studies that have reported death related to *C. auris* infection among COVID-19 patients, the mortality rate was varied from 0% in studies conducted by Gaitan (2020) (31), Puchades (2020) (31), and Zuo et al. (2020), (35) to 75% in Villanueva-Lozano et al. (2020), study (34).

In this meta-analysis using the metaprop function, pooled mortality rate of *C. auris* infection in COVID-19 patients was estimated 37% (95% CI: 15%, 6%; I^2= 58.70%, P= 0.02) (Fig. 2B).

In terms of specific conditions, the pooled mortality rate was more common in COVID-19 patients with diabetes 65% (95% CI: 0.45%, 83%), in taking steroids 43% (95% CI: 18%, 0.69%), >21 days at ICU admission 44% (95% CI: 21%, 0.68%) compared to other strata.

In a sensitivity analysis using user-specified I^2 (25%), we found no significant difference between the pre- and post-sensitivity analysis for the total pooled estimation of the mortality rate of *C. auris* infection; 37% (95% CI: 15%, 61%) versus 36% (95% CI: 9%, 63%), respectively.

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis that investigated the prevalence rate of *C. auris* infection among the COVID-19 patients. According to the latest published studies, the pooled prevalence of *C. auris* infection among COVID-19 patients was 13%. Infection with *C. auris* was more common among patients with >21 days of ICU admission (23%) compared to patients with <21 days, and the unknown group 15%. The pooled mortality of *C. auris* infection in patients with COVID-19 was estimated to be 37%. The risk of mortality was higher among patients with co-existing diabetes (65%), patients under treatment with steroids (43%), and those with more than 21 days of ICU admission (44%).

In a relatively short time, *C. auris* has turned into one of the most serious pathogens within hospital environments. Despite growing awareness about this pathogen, recent outbreaks have occurred in many countries, including those in the Middle East. The first regional case was reported from Kuwait in 2014 (15) followed by several other countries (16-22, 25).

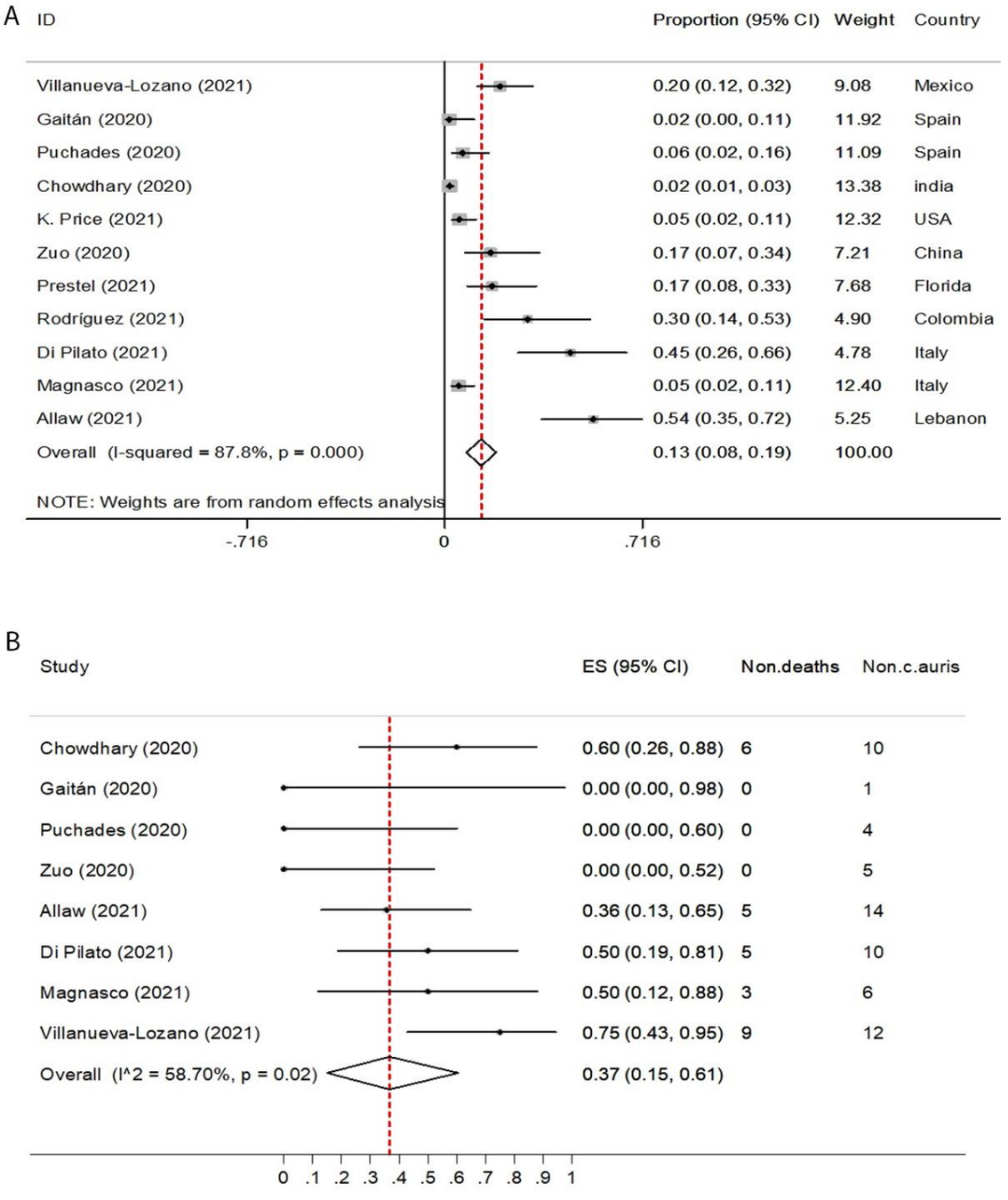

Fig. 2. A) The pooled prevalence of *C. auris* infectionin COVID-19 patients. B) Pooled mortality rate of *C. auris* infection in COVID-19 patients

The transmission of *C. auris* between patients is most likely due to delay in *C. auris* detection and reporting, inadequate handwashing, as well as inadequate cleaning and disinfection of patients' equipment, such as ventilators, and the environment (28). The current COVID-19 pandemic is putting a significant burden on many countries facing a shortage of intensive care units and emergency departments (ED). This burden, however, leads to the optimal application of infection control measures in the ED (28). We found that the prevalence of *C. auris* infection was higher in patients with long-term hospitalization compared with short-term hospitalization. This could be due to the overuse of a wide

range of antibiotics, including piperacillin-tazobactam, carbapenems, and ceftolozane-tazobactam (29, 37). In addition, a longer duration of hospitalization may indicate more severe COVID-19, which could be associated with an increased risk of fungal infections during hospitalization for COVID-19 (33). The pooled risk of mortality was also high in patients receiving steroids, which might be due to increased use of central venous or Foley catheters (29, 38).

Strict infection prevention and control (IPC) measures are needed to prevent further outbreaks of *C. auris* infection in intensive care units. Appropriate diagnostic laboratory methods are critical for the timely detection of *C. auris* in a hospital setting. Improved detection helps in the early administration of antifungal medications for patients and facilitates the timely application of infection control interventions, such as strict isolation, active surveillance of potentially exposed contacts, and also rigorous cleaning and disinfection of patients' equipment and the environment using chlorine-based solutions. Prompt implementation of evidence-based control interventions plays a major role in limiting the dissemination of *C. auris* infection.

This study has some limitations that should be acknowledged. As most of the cases and controls in this study were among hospitalized COVID-19 patients, the estimated prevalence of *C. auris* is probably overestimated. In contrast, the *C. auris* diagnosis is not due to the inabilities of available identification platforms, and some patients might be undiagnosed/under-reported by the included studies in our meta-analysis. Prospective studies with active surveillance would help for the timely diagnosis of this infection.

CONCLUSION

Our study highlights that *C. auris* infection may be an emerging threat during the COVID-19 pandemic, given its high prevalence and rapid transmission in hospital settings. Quick detection and reporting of cases seem essential. A global, national, and regional monitoring program is needed to understand the extent of *C. auris* infection better, evaluate the clade relationship, and guide the implementation of precise IPC strategies to limit the spread of this pathogen in countries.

ACKNOWLEDGEMENTS

The authors wish to thank Shiraz University of Medical Sciences for support us in doing this research.

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