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ORIGINAL ARTICLE

Bacterial and fungal coinfections among patients with COVID-19 in Zanjan, Northwest of Iran; a single-center observational with meta-analysis of the literature

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ABSTRACT

Background and Objectives: There is a poor understanding about the prevalence and characteristics of secondary bacterial and fungal infections among Coronavirus diseases 2019 (COVID-19) superinfection in hospitalized patients.
Materials and Methods: Four hundred COVID-19-proven patients were enrolled in this study. Nasal swabs for molecular assay (Real-time PCR) and sputum samples for further microbiological assays were collected. Following a broad-spectrum search, a meta-analysis was performed using StatsDirect software (version 2.7.9) according to the DerSimonian and Laird method applying the random-effects models.
Results: *Streptococcus* spp. (21.5%) and *Staphylococcus* spp. (16.7%) had the highest prevalence of bacterial coinfection among the COVID-19 patients, while *Acinetobacter* spp. had the lowest prevalence (4.2%). Among fungal coinfections, *Candida albicans* was the most prevalent (6.7%), and *Aspergillus* spp. was the lowest (2%). Males, elderly patients, patients with a history of underlying diseases and drug use, patients who showed acute clinical symptoms, and patients with a prolonged hospital stay had a higher incidence of secondary infections (P-value <0.05). The pooled prevalence for bacterial and fungal coinfections was 33.52% (95% CI: 18.12 to 50.98; I^2: 99.4%; P-value: <0.0001).
Conclusion: We suggest designing additional research with a larger target population and diagnostic molecular analyses to depict a more realistic view of the coinfection status.

Keywords: COVID-19; Secondary infection; Nosocomial infection

INTRODUCTION

Coronavirus diseases 2019 (COVID-19) affect more than 500 million people worldwide, resulting in more than six million deaths (WHO) (1). Up to 2022, over 140,000 of 7 million positive cases have died due to this pandemic in Middle-Eastern Iran (2). A beta-named variant of COVID-19 leads to severe

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acute respiratory syndrome coronavirus 2 (SARS-Cov-2) (3). Early symptoms of SARS-CoV-2 infection are similar to upper respiratory tract infections caused by other microorganisms and include fever, coughing, tiredness, and respiratory discomfort (4-6). Most patients with COVID-19 may have diarrhea, lethargy, myalgia, and anorexia at the outset of the disease (7). Typical symptoms include headaches, dizziness, vomiting, rhinorrhea, and nasal congestion (4-6, 8). Furthermore, the virus can cause significant complications such as respiratory distress syndrome and the involvement of many organs (9).

The broad spectrum of symptoms and their varying incidence period are the main characteristics of COVID-19 infection (6, 10-13). Co-infections of SARS-CoV-2 with bacteria, fungi, and other viruses is a crucial issue that can create a slew of complications in the diagnosis, treatment, and finally exacerbate symptoms and increase death (14, 15). According to investigations, around 5% of COVID-19 patients have COVID-19-associated bacterial (CAB) coinfections during their hospitalization period (14-17). The administration of antibiotics for hospital-acquired bacterial infections caused by *Staphylococcus* spp. and *Streptococcus* spp. is an imperative strategy for the management of hospitalized COVID-19 patients (18). The risk of COVID-19-associated fungal (CAF) coinfections, particularly those caused by *Aspergillus* and *Candida* species, is increased in the target population, especially those admitted to intensive care units (ICU), patients requiring long-term mechanical ventilation, and patients who have been hospitalized for more than 50 days (14-17).

Among hospitalized patients, differentiating COVID-19 infection from hospital-acquired and ventilator-related pneumonia is a matter (19). Additionally, hospitalized patients may develop secondary non-respiratory tract infections, such as urinary tract infections (UTI) and bloodstream infections (BSI) (20). Concurrent bacterial and fungal infections in hospitalized people with COVID-19-induced acute respiratory syndrome are poorly characterized (21). Clinically, distinguishing viral infection from the bacterial or fungal respiratory infection will be problematic (22). Because co-infection with SARS-CoV-2 might increase the effects of primary disease, careful consideration is a critical clinical necessity in patients with COVID-19 (21).

This study aimed to evaluate the prevalence of bacterial and fungal co-infections among patients with COVID-19 in Zanjan-Iran. Also, the meta-analysis of the literature is aimed to compare the results of the current study with previous studies.

MATERIALS AND METHODS

Study settings and data collection. This single-center observational study was conducted in the specialized COVID-19 hospital between February 2020 and February 2021 in Zanjan-Iran.

The following parameters were included in the data collection checklist based on the hospital records: age, gender, history of underlying disease, history of drug use, length of hospital stay, the result of Real-time polymerase chain reaction (PCR) test for SARS-Cov-2 (if available), clinical evidences of secondary infection(s) (including fever, nausea, vomiting, stiff neck, headache, seizures, and other nonspecific symptoms), the color of sputum, and the culture results of sputum (if available) for the diagnosis of secondary infection. This study was approved by the Ethics Committee of Zanjan University of Medical Sciences Code number:IR.ZUMS.REC.1400.179.

Patients and samples. A total of 1390 suspected COVID-19 patients were admitted to the COVID-specialized hospital. Additionally, laboratory evidences of secondary bacterial or fungal infections were captured. Patients with negative Real-time PCR (unconfirmed) were excluded from further analysis.

Assessment of COVID-19 infection by Real-time PCR test. Positive Real-time PCR results were the major inclusion criteria for this study. In this regard, obtained/ordered nasal swab samples were collected from the admitted patients, and RNA extraction and cDNA synthesis were carried out using their kits (YTA; Yekta Tajhiz Azma; Tehran-Iran). Real-time PCR was carried out in triple reactions using Probe qPCR Master Mix (YTA; Yekta Tajhiz Azma; Tehran-Iran). The 2019-nCoV_N1-P primer and probe pairs (FAM-ACC CCG CAT TAC GTT TGG TGG ACC-BHQ1; FAM-ACC CCG CAT /ZEN/ TAC GTT TGG TGG ACC-3IABkFQ) were selected for capturing SARS-Cov-2 during Real-Time processes (CDC).

Microbiological diagnosis of bacterial and fungal pathogens. To detect bacterial and fungal pathogens among patients with clinical signs and symp-

toms, sputum samples were obtained or ordered and cultured on Sabouraud Dextrose Agar (SDA) with chloramphenicol for fungal and Blood agar 5%, Chocolate agar, and MacConkey agar bacterial coinfections. Results were categorized as no sputum obtained, ordered/not done, without growth, contaminated, or based on the recovered organism (s). The cultures were incubated for 3-7 days at 32-37°C. Moreover, potassium hydroxide (KOH), slide culture (for molds), and germ tube production tests for fungal and Gram staining for all specimen were carried out. Moreover, the results of the biochemical tests for bacterial pathogens were recorded.

Meta-analysis and statistical analysis of data. We searched related databases between April 2021 and May 2022 for studies that reported data about COVID-19-associated coinfections. We developed a broad search strategy to identify studies that reported COVID-19-associated coinfections. In our systematic review, the search terms "Coronavirus disease," "COVID-19," "SARS-CoV-2 infection," "Bacterial," "Fungal," "Coinfection,"and related terms and words for relevant studies published in PubMed, Web of Science, Scopus, Google Scholar, LitCovid, and ProQuest between April 2021 and May 2022 were used (Fig. 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. Inclusion criteria were as follows; COVID-19 patients proven with Real-time PCR who have positive for fungal and/or bacterial coinfections. Meta-analysis was performed using StatsDirect software (version 2.7.9) 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 <0·1) and the I^2 statistic (>75 % indicative of "notable" heterogeneity). SPSS (version 20) software was used for analysis. The k2 or independent t-test (Mann-Whitney test) was used to explore the correlation between demographic characteristics and the frequency of laboratory findings. A significance level of 5% was considered.

RESULTS

Patients characteristics. Four hundred patients with confirmed SARS-CoV-2 were identified with secondary fungal and bacterial infections during the study period (between February 2020 and February 2021). Among them,42% were women, and 58% were men (Table 1). Patients aged 30-75 were randomly divided into three groups: 40.5% were >60 years old, 39.3% were 50-60, and 20.3% were under 50 years old (Table 1). Furthermore, 72.5% of patients had a history of underlying disease, and 63.5% had drug administration. Fever, nausea, vomiting, stiff neck, headache, seizures, and other nonspecific symptoms are reported to occur 50.8%, 39%, 22%, 49.3%, 63%, 2.5%, and 9% of the time, respectively. As seen in Table 1, the highest and lowest rates of clinical signs and symptoms were headaches (63 %) and seizures (2.5 %). The patients' mean length of stay (LOS) in hospital wards was 6 to 10 days (64.8%). Furthermore, the sputum colors were as follows: yellow (54%), green (30%), clear (13%), and red or brown sputum in 3% of the patients (Table 1).

Characteristics of secondary bacterial and fungal infections. According to the findings, sputum cultures were positive in 72% of patients. Also, bacterial and fungal species were responsible for 63.2% and 8.8% of secondary infections, respectively. The major bacterial causative agents were as follows; *Streptococcus* spp. (21.5%), *Staphylococcus* spp. (16.7%), *Escherichia coli* (8.7%), *Pseudomonas* pp. (7.2%), *Klebsiella* spp. (4.7%), and *Acinetobacter* spp. (4.2%). Moreover, *Candida albicans* (6.7%) and *Aspergillus* spp. (2,1%) were the dominant fungal pathogens (Table 2). The highest frequency was seen in the age group above sixty years; 75.9% of these patients had a positive culture result (69.7% bacteria and 6.2% fungi) (Table 3). Among patients aged 50 to 60, 74.5% had positive cultures (62.4% of bacteria and 12.1% of fungi) (Table 3). The findings also showed that there was a significant difference in secondary infections between men and women (P-value<0.05) (Table 3). Men had a secondary infection rate of 80.6% (66% for COVID-associated bacterial coninfections, CAB, and 14.6% for COVID-associated fungal infections, CAF), much higher than women at 60.1% (48.3% for CAB and 11.8% for CAF) (P-value< 0.05). Additionally, patients with an underlying condition had a significantly higher secondary infection rate than those without any underlying diseases (total: 84.1%; CAB: 72.8%; CAF: 11.3%, P-value <0.05).

Moreover, patients with a drug administration had

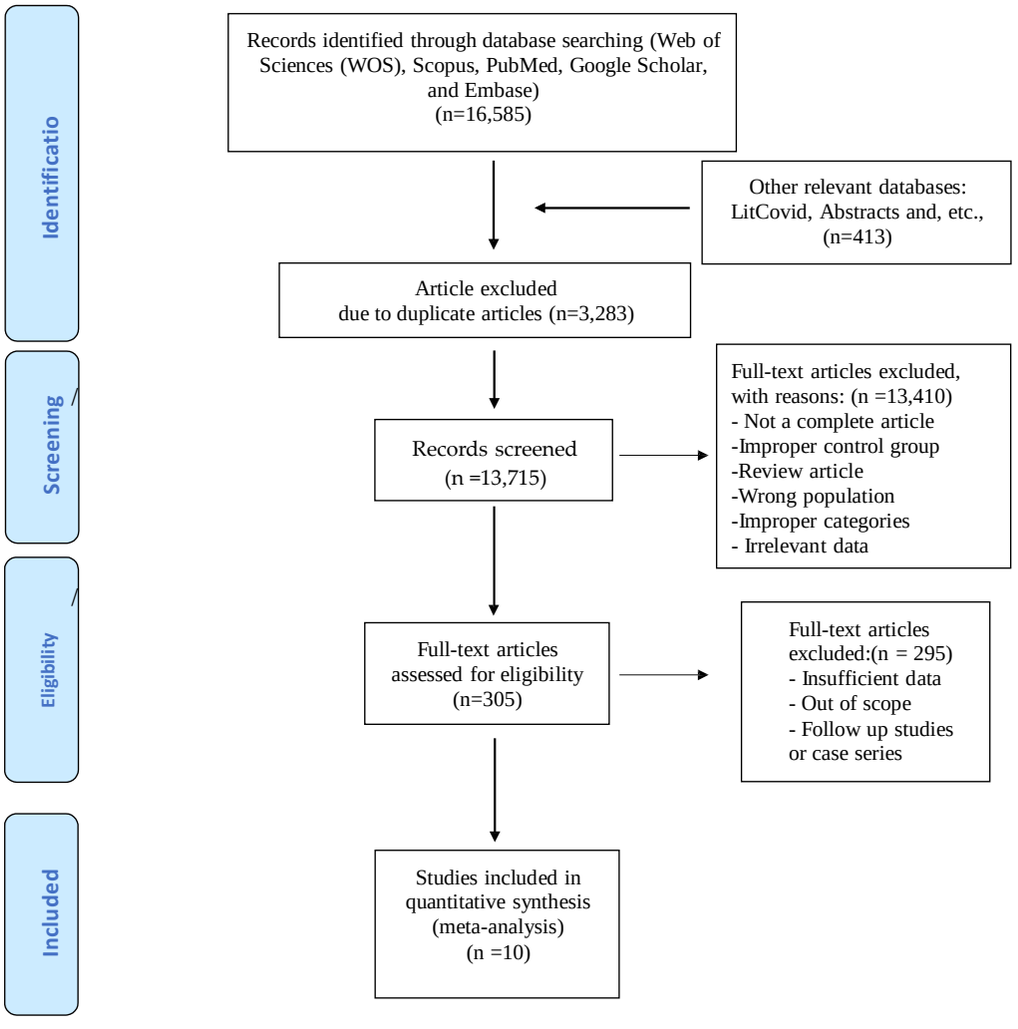

Fig. 1. The flowchart of the study identification and selection process

a significantly higher prevalence of secondary infections (Total: 80.7%; CAB: 75.2%; CAF: 7.5%, P-value< 0.05) (Table 3). Also, patients who spent more than 11 days in the hospital were more susceptible to develop coinfections (total: 95.5%, CAB: 54.6%, CAF: 40.9%, P-value< 0.05) (Table 3). We found a significant difference in clinical symptoms, including fever, nausea, vomiting, headache, neck cramps, and seizures, based on the frequency of secondary infection (P-value: 0.05) (Table 3). According to the findings, patients who experienced the following symptoms were more prone to develop secondary infections (P-value<0.05); fever (81.7%), nausea (64.3%), vomiting (68.2%), headache (94.6%), neck pains (77.2%), and seizures (2.5%) (Table 3).

Meta-analysis. Our meta-analysis included nine eligible studies in the field plus the current study (total of ten studies) (23-31) after an electronic search and removing duplicate and irrelevant records. The distribution of each survey by country is as follows: Spain, USA, Iran, Saudi Arabia, UK, Italy, a multicenter study from Italy, Croatia, Serbia, Slovenia, and two studies from Turkey.

In this analysis, 11,269 patients were hospitalized with SARS-CoV-2. A total of 1,387 CAB coinfections were reported in nine eligible studies. The pooled prevalence for CAB coinfections was 24.08% (95% CI: 15.16 to 34.32; I2: 99.1%; P value: <0.0001) (Tables 4 and 5; Figs. 2 and 3). Also, 475 CAF coinfections were reported in six eligible studies. The pooled prevalence for CAF coinfections was 6.46% (95% CI: 3.47 to 10.27; I2: 95.9%; P value: <0.0001) (Tables 4 and 6; Figs. 4 and 5). The overall prevalence

Table 1. Demographic and clinical characteristics of patients with SARS-CoV-2 and bacterial-Fungal coinfections.

Characteristic	Category	Frequency (N = 400)	Percentage	P-value
Age (years)	>60	162	40.5%	0.03
	50-60	157	39.3%	0.02
	<50	81	20.3%	0.01
Gender	Female	168	42%	0.02
	Male	232	58%	0.03
Comorbidities	Yes	290	72.5%	0.02
	No	110	27.5%	0.04
Underlying Diseases	Yes	254	63.5%	0.01
	No	146	36.5%	0.01
Clinical signs and symptoms	Fever	203	50.8%	0.01
	Nausea	156	39%	0.01
	Vomiting	88	22.%	0.01
	Stiff neck	197	49.3%	0.02
	Headache	252	63%	0.02
	Seizures	10	2.5%	0.02
	Other symptoms	36	9%	0.02
LOS (days)	3-5	119	29.8%	0.001
	6-10	259	64.8%	0.001
	>11	22	5.5%	0.001
Sputum color	yellow	225	54%	0.01
	green	120	30%	0.01
	clear	52	13%	0.01
	red or brown	3	0.75%	

Table 2. Prevalence of bacterial and fungal coinfections isolated from respiratory samples.

Characteristic	Category	Frequency (N = 400)	Percentage	P-value
Sputum culture results	Positive	288	72%	0.04
	Negative	112	28%	0.04
Isolated pathogen	Bacterial	253	63.2%	0.001
	Fungal	35	8.8%	0.001
Bacteria	*Streptococci* spp.	86	21.5%	0.005
spp.	*Staphylococcus* spp.	67	16.7%	0.005
	Escherichia coli	35	8.7%	0.001
	Pseudomonas aeruginosa	29	7.2%	0.001
	Klebsiella spp.	19	4.7%	0.001
	Acinetobacter spp.	17	4.2%	0.001
Fungal spp.	*Candida albicans*	27	6.7%	0.005
	Aspergillus spp.	8	2.1%	0.005

of COVID-19-associated bacterial and fungal coinfections (CABF) in six studies which were occurred concomitantly (not in one patient) was 33.52% (95% CI: 18.12 to 50.98; I2: 99.4%; P value: <0.0001) (Tables 4 and 7; Figs. 6 and 7).

DISCUSSION

During the pre-COVID era, the increase of secondary infections in hospitalized patients has been worrying. With the emergence of the COVID-19

Table 3. Demographic data of patients with fungal and bacterial coinfections.

Characteristic	Category	Frequency bacterial coinfections	Frequency of fungal coinfections	Percentage	P-value
Age	>60	69.7%	6.2%	75.9%	0.04
	50-60	62.4%	12.1%	74.5%	
	<50	51.8%	7.5%	59.3%	
Gender	Female	66%	14.6%	80.6%	0.002
	Male	48.3%	11.8%	60.1%	
Comorbidities	Yes	72.8%	11.3%	84.1%	0.03
	No	47.1%	8.3%	55.4%	
History of antibiotic use	Yes	75.2%	7.5%	80.7%	0.004
	No	36.6%	16.6%	53.2%	
Hospitalization duration (days)	3-5	68.8%	3.5%	72.3%	0.005
	6-10	61.1%	8.8%	69.9%	
	>11	54.6%	40.9%	90.5%	

pandemic, the importance of paying attention to secondary infections has increased. This study aims to clarify the statistics of these infections and guide doctors and public health policymakers in the optimal management of treatment and prevention of COVID-19 patients with secondary infections.

We investigate the frequency of CABF in sputum,urine, blood, and catheter samples of patients admitted to a Covid-specialized hospital in Zanjan-Iran, between February 2020 and February 2021. 58% of patients were men, and 40.5% were >60 years old. A total of 72% of sputum samples were positive for bacterial and fungal systemic infections BFSI. 63.2% of them were bacteria, and 8.8% of them were fungi. The average hospital duration was 6 to 10 days (64.8%).

Studies by Zhang et al. (32) from Shanghai and Liu et al. (33) from the USA indicated that 58% and 54% of the sputum samples were positive for BFSI, respectively. According to Liu et al., this rate increased to 64.9% following intubation (33). We resulted that Gram-positive bacteria, including *Streptococci* spp. and *Staphylococci* spp. were the most common causative agents of BFSI. Hughes et al. (34) and Russell et al. (5) conducted similar research and identified *Staphylococcus aureus* as the most common cause of CAB coinfectionsin the UK. In a study by Ripa et al. (20) in Italy, most of the BSIs were due to Gram-positive pathogens (76/106 isolates, 71.7%), specifically coagulase-negative *Staphylococci* spp. (53/76, 69.7%), while among Gram-negatives (23/106, 21.7%) *Acinetobacter baumanii* (7/23, 30.4%) and *Escherichia coli* (5/23, 21.7%) were predominated.

We found that the rate of BFSI increased with patients' age. This study is in line with those of Zhang et al. (32) in China, Santis et al.(35) in Italy, and Shafran et al.(36). They found that the risk of BFSI in COVID-19 patients rises with age due to physiological and physical circumstances and immunological disorders.

We indicated that the rates of male and female patients with secondary infection were 80.6% (66% bacteria and 14.6% fungi) and 60.1% (48.3% bacteria and 11.8% fungi). However, Zhang et al. (32) reported that the proportion of FBSI cases did not change by the patient’s gender. According to studies by Nasir et al. (37) in Iran and Gebhard et al. (38) in Switzerland, men are more susceptible to acquiring FBSIs when ICU admission rates increase. The variations between the various studies could be related to geographical changes. Another reason is that men and women have physiological and hormonal differences (39).

In contrast to the findings of Zhang et al.(32), we showed that 84.1% of the patients with underlying conditions were BFSI-positive (72.8% bacteria and 11.3% fungi). These discrepancies could be related to the smaller sample size in the Zhang study (57.89%; 22/38) compared to the current study, limiting the data's generalizability. According to a study by Santis et al. (35), 101 patients (40.7%) had BFSI with high severity and extended hospital stay. People with underlying disorders typically have a weakened immune system and are more susceptible to coinfections. According to Cullen et al. in Dublin, BFSIs were more common in hospitalized patients

Table 5. Analysis details of the eligible studies.

Stratum	Standardized effect	Variance	% Weights (fixed, random)		Studies
1	0.084693	0.000627	14.33194	11.461798	Moreno-Torres; 18 Aug 2021; Spain
2	0.084233	0.00072	12.489326	11.452664	Scott; 13 Sep 2021; USA Moradi;
3	0.076492	0.000181	49.710125	11.506068	Nov 2021; Iran
4	0.114618	0.00166	5.415487	11.360675	Genç Bahçe; 15 Jan 22; Turkey
5	0.169028	0.001012	8.884994	11.423936	Papst; 28 Jan 2022; Slovenia-Serbia-Italy-Croatia
6	0.529412	0.028986	0.310098	9.210304	Alqahtani; 19 Feb 2022; Saudi Arabia
7	0.304348	0.002554	3.518943	11.274505	Chan; 23 March 2022; UK Ceparano;
8	0.445596	0.005168	1.739248	11.030054	28 March 22; Italy Current Study
9	0.6325	0.002497	3.599838	11.279995	

Table 4. Pooled prevalence, heterogeneity, and publication bias analyses results with details.

Variables & Risk Factors	# Of study	# of Bacterial coinfections among eligible COVID patients	Prevalence (95% CI)	Heterogeneity			Publication bias				
							Egger's test			Begg's test	
				I^2 (%)	Cochran Q	Significance Level (P-value)	Bias	95% CI	Significance Level (P-value)	Kendall's Tau	Significance level (P-value)
COVID-Bacterial coinfection	8	1,387 in 11,121	24.08% (95% CI: 15.16 to 34.32	99.1	910.511	P < 0.0001	11.22	3.77 to 18.68	P = 0.0092	0.666	P = 0.0127
COVID-Fungal coinfection	6	475 in 7,873	6.46% (95% CI: 3.47 to 10.27	97.9	146.593	P < 0.0001	2.44	-6.29 to 11.18	P = 0.5044	0.4285	P = 0.2389
Overall Bacterial and Fungal coinfections among COVID-19 patients	6	1,564 in 8,104	33.52% (95% CI: 18.12 to 50.98	99.4	810.096	P < 0.0001	14.43	2.11 to 30.98	P = 0.0726	0.6	P = 0.1361

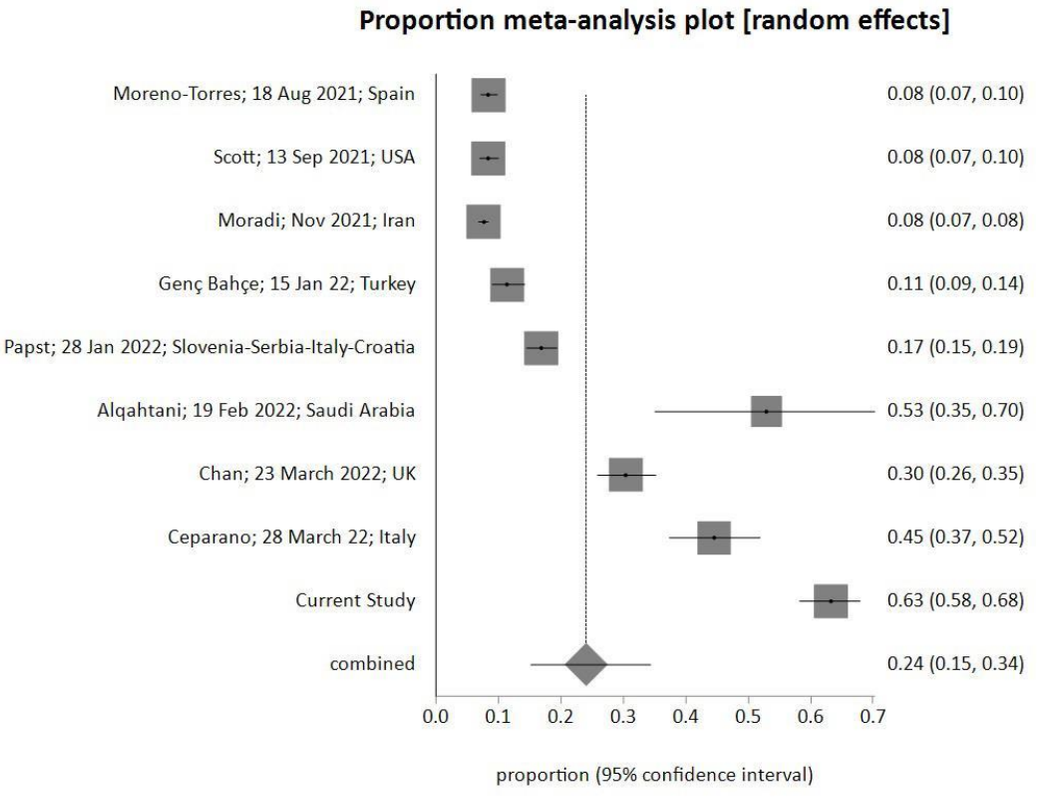

Fig. 2. Forest plot of the pooled prevalence of patients with COVID-19 and bacterial coinfections.

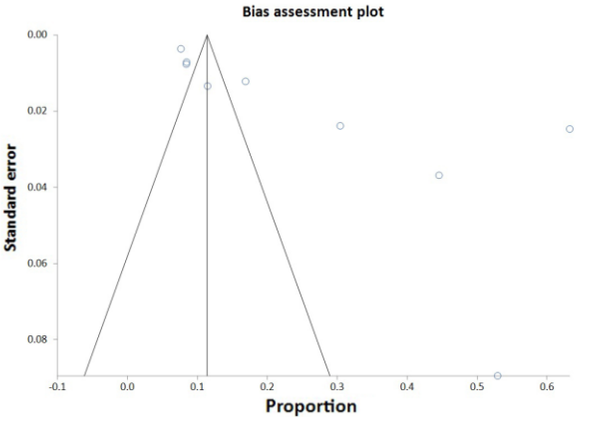

Fig. 3. Funnel plot of the pooled prevalence of patients with COVID-19 and bacterial coinfections.

with a history of drug administration (40). Patients with a history of drug use were found to have a secondary infection in 80.7% of cases (75.2% of bacteria and 7.5% of fungi). According to the findings of this study, the length of hospital stay impacts the incidence of secondary infection. This finding was in line with the results reported by Zhang et al. and Nasir et al.'s (32, 37).

We indicated that patients having COVID-19 had more severe clinical symptoms and positive culture results indicating BFSI. This is in line with the findings of investigations by Zhang et al. and Gebhard et al. (32, 38). These findings can be explained by the fact that the secondary infection exacerbates the disease symptoms, and it is expected that the symptoms of patients with the secondary infection will be more severe than those of patients with COVID-19 alone. *Candida albicans* was the major fungus responsible for FBSI (6.7%). According to a study by White et al. in the UK (41), 1.3% of patients with COVID-19 had severe *Candida* infection. A study indicated that the prevalence of emerging multi-drug resistant *C. auris* among COVID-19 patients was 5.7% (42). Other investigations revealed that 2.2 to 12% of patients with COVID-19 had *Candida* infection.

Moreover, our results from the meta-analysis showed that bacterial coinfection occurred 2.15 times more than fungal infections among COVID-19 patients. Although they were frequently fatal causes of influenza pandemics and made viral respiratory illnesses worse, bacterial coinfections have not been thoroughly studied in individuals with coronavirus

Table 6. Analysis details of studies with fungal coinfections.

Stratum	Standardized effect	Variance	% Weights (fixed, random)		Studies
1	0.062568	0.000181	66.991703	15.392049	Moradi; Nov 2021; Iran
2	0.019934	0.00166	7.298165	14.72316	Genç Bahçe; 15 Jan 22; Turkey
3	0.015182	0.001012	11.973836	15.008993	Papst; 28 Jan 2022; Slovenia-Serbia-Italy-Croatia
4	0.189189	0.006734	1.798801	12.812763	Arasteh; 13 Feb 2022; Turkey
5	0.02046	0.002554	4.742293	14.346078	Chan; 23 March 2022; UK
6	0.160622	0.005168	2.343892	13.347263	Ceparano; 28 March 22; Italy
7	0.0875	0.002497	4.851311	14.369694	Current Study

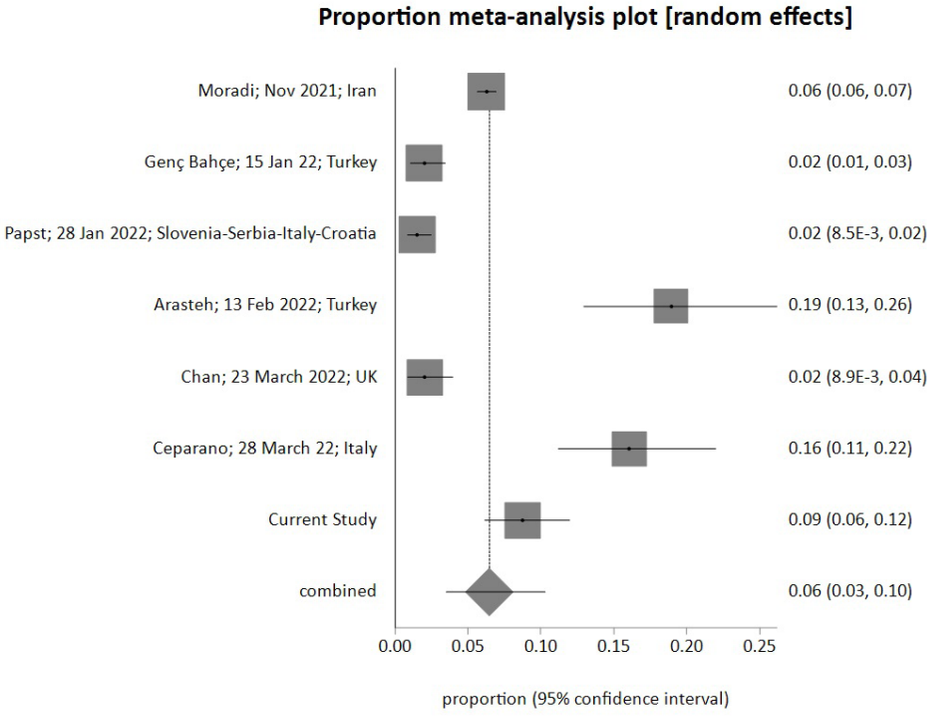

Fig. 4. Forest plot of the pooled prevalence of patients with COVID-19 and fungal coinfections.

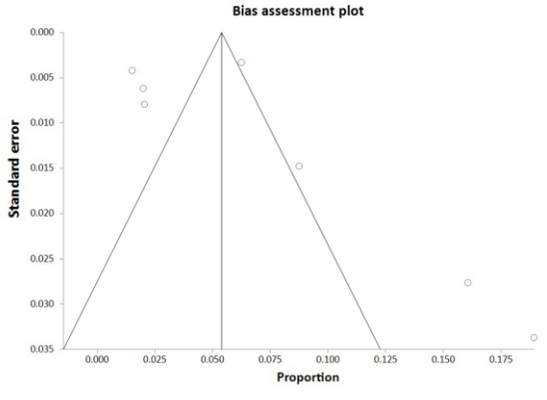

Fig. 5. Funnel plot of the pooled prevalence of patients with COVID-19 and fungal coinfections.

disease (COVID-19). Numerous viral respiratory tract infections frequently result in bacterial coinfection, dramatically increasing morbidity and death (43). Increasing published evidence should warn clinicians about the link between COVID-19 and invasive fungal infections (IFIs) (44). IFIs are known to increase mortality significantly and can exacerbate the clinical course of COVID-19, particularly in critically ill patients admitted to the ICU. Secondary IFIs, typically found in individuals with severe immunodeficiency, indicate that SARS-CoV-2 can overwhelm the host immune system (44, 45).

One of our study's limitations is that we carried out a single-center investigation. Another limitation is

Table 7. Analysis details of studies with bacterial and fungal coinfections.

Stratum	Standardized effect	Variance	% Weights (fixed, random)		Studies
1	0.13906	0.000181	68.218823	16.836064	Moradi; Nov 2021; Iran
2	0.134551	0.00166	7.431849	16.709549	Genç Bahçe; 15 Jan 22; Turkey
3	0.184211	0.001012	12.193166	16.764757	Papst; 28 Jan 2022; Slovenia-Serbia-Italy-Croatia
4	0.324808	0.002554	4.82916	16.633945	Chan; 23 March 2022; UK
5	0.606218	0.005168	2.386826	16.41691	Ceparano; 28 March 22; Italy
6	0.72	0.002497	4.940175	16.638775	Current Study

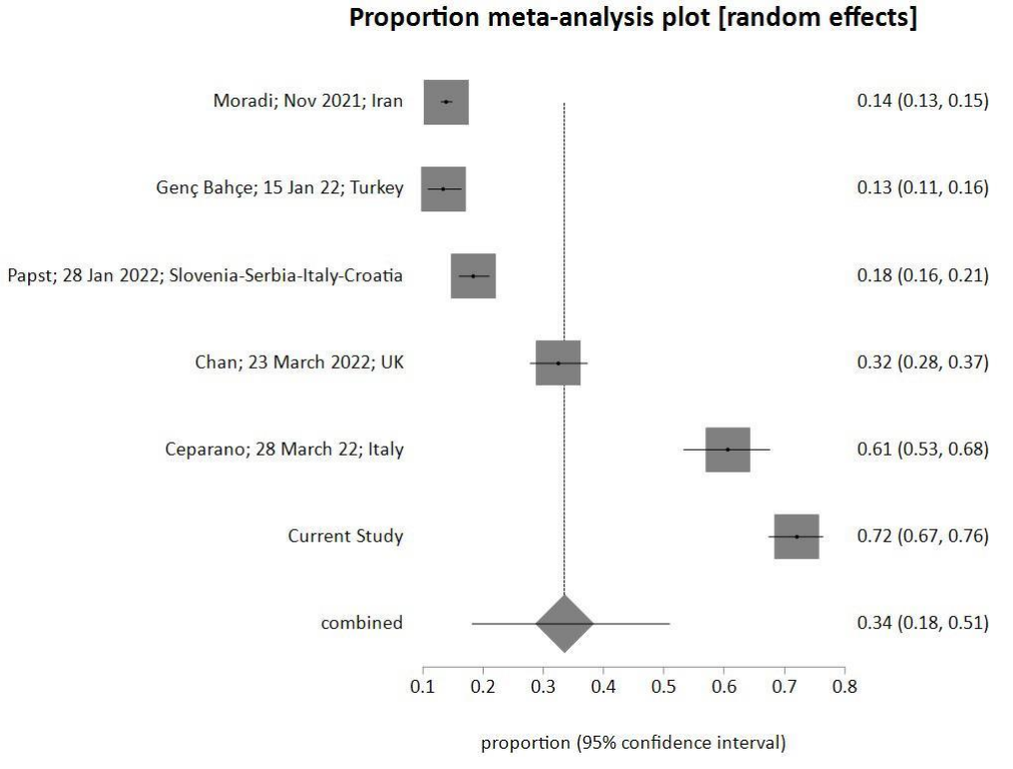

Fig. 6. Forest plot of the pooled prevalence of patients with COVID-19 and fungal and bacterial coinfections.

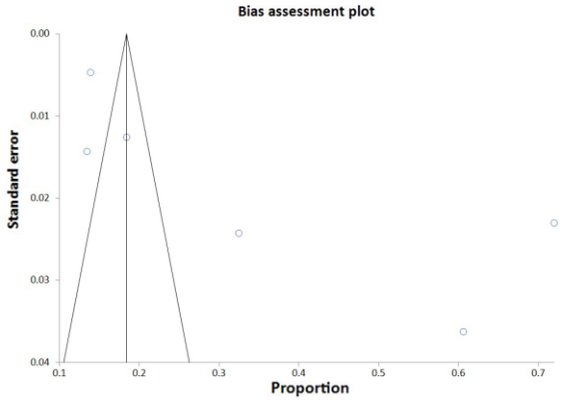

Fig. 7. Funnel plot of the pooled prevalence of patients with COVID-19 and fungal and bacterial coinfections.

that we could not perform a cohort study due to limitations in accessibility to patients and data during the quarantine. However, we reported the status of COVID-19-associated fungal and bacterial coinfection on a large scale from northwest Iran. Also, the application of Real-time PCR and performing a comprehensive meta-analysis are other strengths of our investigation.

CONCLUSION

We showed that COVID-19 patients with secondary bacterial and fungal co-infections were mainly old-

er men having underlying diseases and patients with obvious clinical signs of respiratory failure. Bacteria were also more than half of the identified respiratory pathogens. Therefore, early detection of secondary infection, identifying high-risk patients, and determining appropriate interventions to reduce mortality is essential. Finally, similar studies supported by molecular diagnostic methods, more extensive scales, and more medical centers are recommended.

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