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SYSTEMATIC REVIEW AND META-ANALYSIS

Diversity in Fungal Infections in the Initial Waves of COVID-19: An Occurrence Based Systematic Review

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ABSTRACT

Background: Fungal coinfections have been part of the complications in coronavirus disease (COVID-19) patients. While systematic reviews on individual fungus was available, comprehensive data on the occurrence of various fungal infections was limited.

Methodology: A systematic search in the databases 'PubMed' and 'Global Research Database on COVID-19 by the World Health Organization (WHO) was made using relevant search terms. Only fungal coinfections/superinfections in confirmed COVID-19 cases were considered. All observational studies, case series, and case reports in English were included. Overall, the occurrence of the fungal infections and the associated factors was noted. Chi-square and Fisher's exact tests compared epidemiological factors between survived and dead.

Results: Data from 126 eligible studies reporting 870 cases showed that mucormycosis was the most common infection (42.5%), followed by aspergillosis (32.41%) and candidiasis (22.87%). The majority of the infections were seen in severe COVID-19 (94.01%), in ICU (67.25%), and with mechanical ventilation (73.61%). Prior steroid therapy was seen in 81.3% in mucormycosis. In aspergillosis, mechanical ventilation, infection due to *Aspergillus fumigatus* and administration of steroids at more than the recommended dose were significantly associated with those who died ($p<0.05$).

Conclusion: Mucormycosis, followed by invasive pulmonary aspergillosis and invasive candidiasis, has been the most common coinfections/superinfections in COVID-19 patients. Early diagnosis led to better survival in Covid associated mucormycosis (CAM); however, in COVID-19-associated pulmonary aspergillosis (CAPA), mechanical ventilation, larger doses of corticosteroids than recommended and infection with *A. fumigatus* were significant associations among those who succumbed to the condition.

KEYWORDS: Aspergillosis, candidiasis; Coinfections; Superinfections COVID-19; Pandemic; Mucormycosis

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) brought a plethora of other related complications in the susceptible hosts. With the limitless hospital admissions due to the virus, a massive increase in healthcare-associated infections (HAI) with opportunistic pathogens was witnessed in the form of several bacterial and fungal infections.[1,2] There have been several original studies and reviews on this aspect of coinfections in COVID-19 patients. [3, 4] The best example of this crisis was the unprecedented rise in mucormycosis cases during the second wave of the

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pandemic in India.[5] Studies have shown several predisposing risk factors associated with the fungal coinfections.[6, 7]

While most of the systematic reviews have focused on a single fungal pathogen,[8-10], this systematic review was performed to get comprehensive data on the various fungal infections across the globe in COVID-19 patients published in literature since the beginning of the pandemic.

METHODOLOGY

Search strategy

A systematic search was performed in two electronic databases 'PubMed' and 'Global research database on COVID-19 by the World Health Organization (WHO)'. Articles published between January 01, 2019, to June 15, 2021 were searched by using the following search terms: The PubMed database was searched using advanced search tool with the MeSH terms entered as ((((((((((Covid-19) OR (COVID-19)) OR (Coronavirus disease))) AND (Fungal diseases)) OR (Fungal coinfections)) OR (Secondary fungal infections)) OR (Covid associated mucormycosis)) OR (Mucormycosis)) OR (Candidiasis)) OR (Aspergillosis)) OR (Aspergillus), while the WHO database was searched using the search terms (Covid-19 OR COVID-19 OR Coronavirus disease) AND (Fungal diseases OR Fungal coinfections OR Secondary fungal infection OR Covid associated mucormycosis OR Mucormycosis OR Candidiasis OR Aspergillosis OR Aspergillus).

Definitions and standard recommendations

Coinfection was defined as the recovery of another respiratory fungal pathogen along with SARS-COV-2 when COVID-19 was diagnosed. Superinfection was defined as the subsequent recovery of pathogens during COVID-19 treatment and care.[4] The severity of COVID-19 was classified according to WHO standards.[11] WHO recommended choice for corticosteroids in severe COVID-19 only at recommended doses of 32mg methylprednisolone per day or its equivalent (6mg dexamethasone per day or 50mg hydrocortisone every 8 hours) for 7 – 10 days in severe COVID-19 was taken as reference.[12] Microbiological evidence of fungal infections in the form of microscopy, culture, molecular methods, and serological assays were noted to support a diagnosis of infection.

Inclusion and Exclusion criteria

All articles in the English language on fungal coinfections or secondary fungal infections in patients with COVID-19 were included. Cases of COVID-19 confirmed by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) only were considered.

Reviews, editorials, opinions, and research protocols without primary data were excluded. Articles with missing data on patient profiles and other variables were not considered. Reports of fungal infection without microbiological evidence of infection and reports of fungal colonization were excluded. Any retrospective data without mentioning the precise classification of the fungal isolation procedure was not included.

All grades of COVID-19-associated pulmonary aspergillosis (CAPA) by the European Organization for Research and Treatment of Cancer (EORTC) were considered for aspergillosis infections.[13]

Study selection

Two independent authors (AS and SS) screened the abstract of the studies. Two authors (TB and AS/SS) reviewed the full texts of the selected abstracts for eligibility. Any discrepancy or ambiguity was resolved by consensus. References cited by the articles and articles citing the selected articles were also checked for eligibility. Reporting was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.[14] The review protocol was registered in the PROSPERO register (CRD42021286172).

Data extraction

The two independent reviewers (TB and AS/SS) extracted data from the selected studies using a Microsoft Excel spreadsheet. Data was doubly checked for accuracy.

The following data was retrieved from all the studies, as per availability, study design, period/year of study, publication date, country of origin, number of cases studied/reported, age, gender, ICU admission, mechanical ventilation, history of diabetes mellitus, hypertension, obesity, malignancy, chronic obstructive pulmonary disease (COPD), number of days of fungal infection post-COVID-19, COVID-19 severity, fungal diagnosis, mode of diagnosis, fungal species, bacterial coinfection, steroid therapy, type of steroid therapy, dose of steroids used, average days of steroid therapy, prior antibiotic therapy, antibacterial treatments, antifungal treatments and outcome.

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Data synthesis and Statistical analysis

The primary outcome assessed was the proportions of fungal infections reported as co infections or superinfections in COVID-19 and their associated factors. Data was also stratified according to the global distribution of these reports in three six monthly intervals since the inception of the pandemic, i.e. January – June 2020, July - December 2020 and January - June 2021.

Heterogeneity (I2) was graded on high, substantial, moderate and low levels based on the I2 values ranging from 75-100%, 50-90%, 30-60% and below 40%, respectively.[15] The funnel plot was used to evaluate the publication bias (Annexure 1). Categorical variables were expressed as relative frequencies and proportions while continuous variables as mean or median with dispersion using Medcalc® statistical software (version: 19.6.3.0)

Further, for those infections like aspergillosis and mucormycosis with sufficient data (≤ 5 parameters), clinical characteristics were compared between the survived and the dead with the Chi-square test and Fisher's exact test in Medcalc® statistical software (version: 19.6.3.0). While calculating the overall occurrence, fungal cases with mixed infections were also included.

RESULTS

Screening of studies

A total of 1777 search articles were screened, of which 126 articles finally qualified for systematic review. The flowchart for the selection of the studies is shown in Figure 1. A total of 126 studies constituted 870 cases of fungal infections. [16-141]

The studies included in the analysis comprised Case reports (n=84), Cross-sectional studies (n=19), Cohort studies (n=11), Case series (n=8), Case-control studies (n=3) and Abstract only (n=1). The lists of included and excluded studies have been shown in Annexure 2 and Annexure 3.

These were distributed as 48 studies comprising 220 cases, 45 studies comprising 424 cases, and 33 studies comprising 226 cases in the three study periods. The majority of fungal infections were reported from France (7), the United States (11) and India (9) in January – June 2020, July - December 2020 and January - June 2021 periods, respectively. The distribution of the studies of different fungal infections in different study periods is shown in Figure 2.

Figure 1: PRISMA flowchart showing selected studies

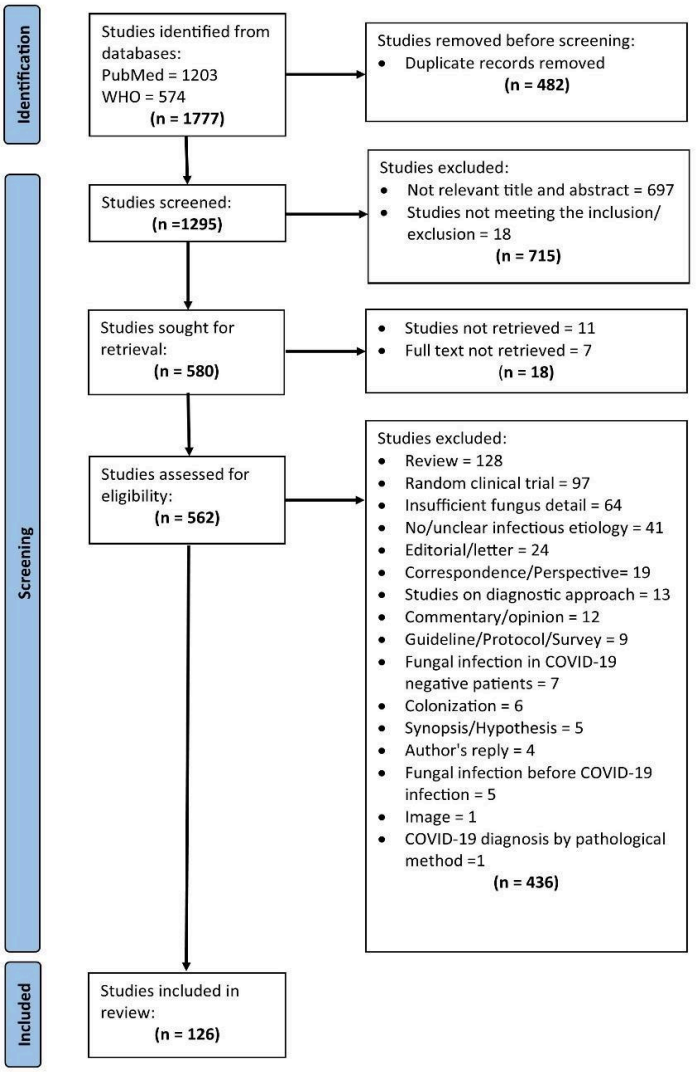
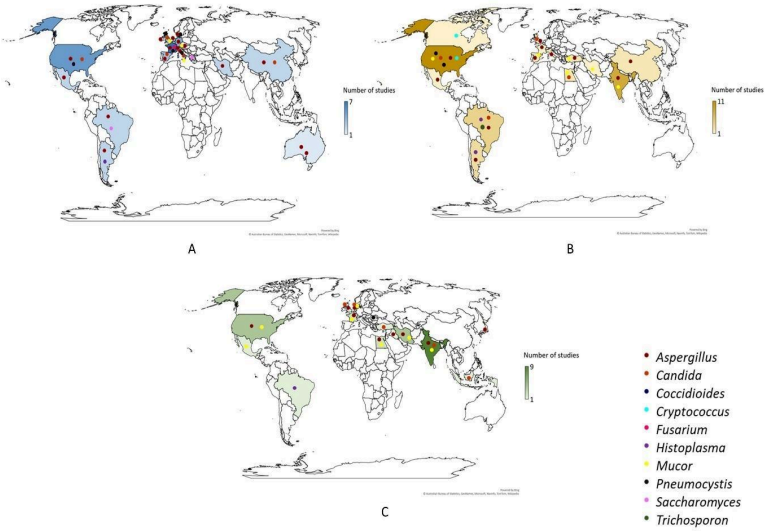


Figure 2: Distribution of studies (A: Jan-2020 to Jun-2020; B: Jul-2020 to Dec-2020; C: Jan-2021 to Jun-2021) of different fungal infections in COVID-19 patients across the globe



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Occurrence of fungal infections

A total of 10 different types of fungal infections in COVID-19 were reported. The overall summary of epidemiological factors of fungal infections in COVID-19 patients has been shown in Table 1.

Table 1: Overall prevalence summary of epidemiological factors of fungal infections in COVID-19 patients

Parameter	Studies (N)	Sample size(N)	Positive cases (n)	Occurrence % (95% CI)
Total	126	870	870	-
Male	110 [16-30,32-38,40-44,46-59,61-64,68-69,71-82,84-106, 108,111-112,114-116,119-121,123-141]	549	370	67.39 (63.30-71.31)
Female	110 [16-30,32-38,40-44,46-59,61-64,68-69,71-82,84-106, 108,111-112,114-116,119-121,123-141]	550	180	32.72 (28.82–36.82)
Mucor	37 [16-45,105,115-116,118-121]	870	370	42.52 (39.22-45.89)
Aspergillus	63 [46-99,101,105-106,115-116,118-121]	870	282	32.41 (29.31–35.64)
Candida	18 [100-114,122-124]	870	199	22.87 (20.12-25.81)
Pneumocystis	7 [126-132]	870	16	1.83 (1.05-2.97)
Histoplasma	4 [133-136]	870	5	0.57 (0.19-1.34)
Trichosporon	1 [141]	870	5	0.57 (0.19-1.34)
Saccharomyces	2 [123,139]	870	3	0.34 (0.07-1.00)
Coccidioides	1 [137]	870	1	0.11 (0.00-0.60)
Cryptococcus	2 [125,138]	870	2	0.22 (0.03-0.83)
Fusarium	1 [140]	870	1	0.11 (0.00-0.60)
ICU admission	100 [16-28,34-39,41-44,46-48,50-57,81,85,87-88,91-101, 103-109,111-113,115-116,119-120,123-128,130-139 ,141]	568	382	67.25 (53.21 –60.76)
Mechanical Ventilation	77 [16-17,19-22,25-26,28,36-39,41-44,46-48,52,54-68,7 1,73-77,79-81,84,87,90-91,93-98,103-104,106-107,1 11-112,115,119-120,123-124,126,130-133,135-137, 139-141]	398	293	73.61 (69.0 – 77.88)
Severe COVID-19 status	78 [16-21,24-25,27-28,38-39,41-43,46-49,53-57,60-69,7 2-74,85-86,88,91,93-94,96,98,100-109,111,114-116, 119,124-128,130-135,137-141]	384	361	94.01 (91.15 – 96.)
Diabetes	120 [16-30,32-44,46-109,111-116,119-121,123-141]	635	253	39.84 (36.01 – 43.77)
Hypertension	120 [16-30,32-44,46-48,90-109,111-116,118-121,123-14 1]	653	266	40.73 (36.94 – 44.62)

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COPD	119 [16-30,32-44,46-75,77-88,90-109,111-116,118-121,123-141]	652	91	13.95 (11.39 – 16.86)
Obesity	120 [16-30,32-44,46-62,64-82,84,86-88,90-100,102-109,111-116,118-121,123-141]	625	81	12.96 (10.43 – 15.85)
Malignancy	117 [16-22,24-30,32-44,46-84,86-88,90-100,102-109,111-116,118-121,123-141]	626	46	7.34 (5.43 – 9.68)
Bacterial coinfections	78 [16-25,28,30,33,40-41,43-44,46-58,60,63,66,71-72,74,76-77,81,92-101,103,106,108-112,115,119-120,124-130,132-141	426	40	9.38 (6.79 – 12.57)
Antibiotic treatment	97 [16-22,24,28,30,32-33,35-37,41-44,46-59,61-64,68-69,71-77,79-82,84,87-91,93-97,99-100,102-104,106,108-116,118-120,123-130,132-141]	452	272	60.17 (55.50 – 64.72)
Antifungal treatment	101 [16-22,24-28,30,32,34-44,46-64,68-69,71-75,79-81,86-89,92-96,99-100,102-107,109-112,114-116,119-121,123-141]	388	303	78.09 (73.64 – 82.11)
Steroid therapy	102 [16-26,28,30,32-37,41-44,46-63,66,68-69,71-81,84,87-90,92,111-116,118-121,124-141]	572	324	56.64 (52.47 – 60.75)
Survived	104 [16-21,23-28,30,32-44,46-58,60-64,66, 68-69,71-75,77-82,84,86,88,90-100,102,104-107,111-112,114-116,119-121,123-141]	426	217	50.93 (46.08 – 55.78)
Died	104 [16-21,23-28,30,32-44,46-58,60-64,66, 68-69,71-75,77-82,84,86,88,90-100,102,104-107,111-112,114-116,119-121,123-141]	426	209	49.06 (44.22 – 53.92)
Phenotypic (Microscopy, Culture, Autopsy, Biopsy)	98 [16-22,25-28,30,32,34-43,46-59,61-64,66-69,71-72,75-78,80-81,84,87-96,99-101,103-105,107-109,111,113-116,119-121,124-131,133-141]	492	398	80.89 (77.14 – 84.28)
Molecular (PCR, MALDI-TOF)	98 [16-22,25-28,30,32,34-43,46-59,61-64,66-69,71-72,75-78,80-81,84,87-96,99-101,103-105,107-109,111,113-116,119-121,124-131,133-141]	492	50	10.16 (7.64 –13.18)
Immunological/ Serological	98 [16-22,25-28,30,32,34-43,46-59,61-64,66-69,71-72,75-78,80-81,84,87-96,99-101,103-105,107-109,111,113-116,119-121,124-131,133-141]	492	232	47.15 (42.67 – 51.67)

ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease; MALDI-TOF: Matrix-Assisted Laser Desorption/Ionization-Time Of Flight; [references of studies included in proportion analysis]

Among the fungal infections, the proportion of mucormycosis cases was highest (370, 42.5%), followed by aspergillosis (282, 32.4%) and candidiasis (199, 22.8%). Other fungal pathogens reported were *Pneumocystis jiroveci* (16, 1.8%), *Histoplasma capsulatum* (5, 0.5%), *Trichosporon asahii* (5, 0.5%), *Saccharomyces* spp. (3, 0.3%), *Cryptococcus neoformans* (2, 0.2%), *Fusarium proliferatum* (1, 0.1%), and *Coccidioides immitis* (1, 0.1%).

The majority of the cases of fungal infections were seen in patients with severe COVID-19 (361, 94%) with ICU admission (382, 57%) and on mechanical ventilation (293, 73.6%). Nearly 40% of the cases had diabetes

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mellitus (253/635) and hypertension (266/653). Steroid therapy as a part of COVID-19 treatment was given in 56.6% (324/572) cases. Dexamethasone was the most commonly used agent (77, 52.02%). Bacterial coinfection was seen in only 8.7% (40/426), but antibiotic treatment was given in 60.1% (272/452) cases. Multimodal diagnostic methods were used for fungal infections with a maximum employing microscopy and culture (398, 80.8%). The data on individual fungal infections are as follows:

Mucormycosis

Thirty-one studies reported a single infection due to COVID-19-associated mucormycosis (CAM), adding up to 329 cases. Among these, rhino orbital ocular mucormycosis was seen in 321 (97.56%) cases, pulmonary in 5 (1.51%) cases, and 1 (0.3%) case each of disseminated gastrointestinal and skeletal. The prevalence summary of epidemiological factors of *Mucor* in CAM has been included in Table 2.

Most cases were reported from India in the study period Jan-Jun 2021.

Table 2: Prevalence summary of epidemiological factors of *Mucor* in COVID-19 associated mucormycosis (CAM)

Parameter	Studies	Sample size (N)	Positive cases (n)	Occurrence % (95% CI)
Male	27 [16-30,32-38, 40-44]	91	65	71.42 (61.00-80.41)
Female	27 [16-30,32-38, 40-44]	91	26	28.57 (19.59-39.00)
ICU admission	23 [16-28,34- 39,41-44]	94	24	25.53 (17.09-35.37)
Severe COVID-19 status	15 [16-21,24-25,27-28,38-39,41-43]	50	34	68.00 (53.30-80.48)
Mechanical Ventilation	17 [16-17,19-22,25-26,28,36-39,41-44]	66	23	34.84 (23.53-47.58)
Diabetes	28 [16-30, 32-44]	101	81	80.19 (71.09-87.46)
Hypertension	28 [16-30, 32-44]	101	45	44.55 (34.66-54.78)
COPD	28 [16-30, 32-44]	101	5	4.95 (1.63-11.18)
Obesity	27 [16-22,24-30,32-44]	78	3	3.84 (0.80-10.83)
Malignancy	27 [16-22,24-30,32-44]	78	4	5.12 (1.41-12.61)
Steroid therapy	23 [16-26,28, 30, 32-37,41-44]	86	70	81.39 (71.55-88.98)
Survived	25 [16-21, 23-25,27-28, 30, 32-44]	93	58	62.36 (51.72-72.21)
Died	25 [16-21, 23,25,27-28, 30, 32-44]	93	35	37.63 (27.79-48.28)

ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease; [references of studies included in proportion analysis]

The mean age of the patients was 55.99 ± 0.07 years, and male to female ratio was 2.5:1. Among the patients with mucormycosis, ICU admission (24, 25.5%), severe COVID-19 (34, 68%), history of diabetes (81, 80.1%), hypertension (45, 44.5%) and malignancy (4, 5.1%) was seen. Steroid use during COVID-19 in these cases was seen in 81.3% (70/86) of the cases. Mortality was reported in 37.6% (35/93) of the cases.

It was interesting to note that cases of mucormycosis were reported in Australia, Italy and the UK (3 studies) during the initial period of the pandemic, which gradually increased to 8 studies from Brazil, Egypt, Spain, the USA, Iran and Turkey during the period Jul-Dec 2020. Finally, 13 studies were found in the Jan-Jun 2021 period, with the maximum cases reported

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from India (278,75.13%). The majority of the studies did not mention the species of *Mucor*.

On comparison of the demographic and associated factors of those who survived and died with CAM, it was found that though cases with ICU admission (11, 20.37%), severe COVID-19 (16, 37.20%), mechanical ventilation (6, 13.04%), hypertension (15, 19.48%) was found more among those who died, prevalence of diabetes mellitus was comparable in both the groups (Table 3).

However, the diagnosis of CAM as coinfection with COVID-19 was more (5, 71.42%) in those who survived.

Aspergillosis

For aspergillosis, a total of 282 cases were reported in 63 studies. Studies on aspergillosis were distributed throughout the globe during the entire pandemic. The prevalence summary of epidemiological factors of *Aspergillus* in CAPA has been included in Table 4

Table 3: Comparison of epidemiological and clinical characteristics of patients with COVID-19-associated mucormycosis (CAM) (Survived v/s Died)

Parameters	Total	Survived (%)	Died (%)	P value
Number	79	39 (49.36)	38 (48.10)	
Not mentioned		*2 (2.5)*		
Demographic data				
Age	77	56.05 ±14.01	55.94 ±12.26	1.00
Male	58	28 (48.27)	30 (51.72)	0.46
Female	19	11 (57.89)	8 (42.10)	
Risk factors				
ICU admission	54	4 (7.40)	11 (20.37)	0.13
Not mentioned	*19*	*11 (57.89)*	*8 (42.10)*	
Severe COVID-19 status	43	10 (23.255)	16 (37.20)	0.53
Not mentioned	*34*	*20 (58.82)*	*14 (41.17)*	
Mechanical ventilation	46	2 (4.34)	6 (13.04)	**0.43**
Not mentioned	*31*	*20 (64.51)*	*11 (35.48)*	
Diabetes	64	24 (37.5)	23 (35.93)	1.00
Not mentioned	*13*	*7 (53.84)*	*6 (46.15)*	
Hypertension	77	12 (15.58)	15 (19.48)	0.47
COPD		1 (1.29)	4 (5.19)	0.19
Malignancy		1 (1.29)	3 (3.89)	0.35
Renal Failure		4 (5.19)	7 (9.09)	0.34
Chronic sinusitis		1 (1.29)	0	1.00
Bacterial coinfection	46	1 (2.17)	1 (2.17)	1.00
Not mentioned	*31*	*19 (61.29)*	*12 (38.70)*	
Antibiotic treatment	45	8 (17.77)	12 (26.66)	0.76
Not mentioned	*32*	*19 (59.37)*	*13 (40.62)*	
Antifungal treatment	76	35 (46.05)	33 (43.42)	0.71
Azoles		3 (3.94)	2 (2.63)	1.00
Echinocandin		0	2 (2.63)	0.24
Amphotericin-B		35 (46.05)	31 (40.78)	0.34
Not mentioned	*1*	*0*	*1 (100)*	
Steroid therapy	73	27 (36.98)	29 (39.72)	1.00
Not mentioned	*4*	*4 (100)*	*0*	
<10 days	32	6 (18.75)	11 (34.37)	1.00
Not mentioned	*45*	*24 (53.33)*	*21 (46.66)*	
>10 days	32	2 (6.25)	6 (18.75)	0.22
Not mentioned	*45*	*24 (53.33)*	*21 (46.66)*	
More than the recommended dose	11	2 (18.18)	5 (45.45)	**1.00**
Not mentioned	*66*	*36 (54.54)*	*30 (45.45)*	
Infection days post COVID infection				
Coinfection	7	5 (71.42)	2 (28.57)	0.22
Average number of days	40	20.94 ±18.73	20.80 ±18.32	1.00
Not mentioned	*30*	*17 (56.66)*	*13 (43.33)*	

ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease

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Table 4: Prevalence summary of epidemiological factors of *Aspergillus* in COVID-19-associated pulmonary aspergillosis (CAPA)

Parameter	Studies	Sample size (N)	Positive cases (n)	Occurrence % (95% CI)
Male	49 [46-59,61-64,68-69,71-99]	213	150	70.42 (63.80-76.46)
Female	49 [46-59,61-64,68-69,71-99]	213	63	29.57 (23.54-36.20)
ICU admission	44 [46-48,50-77,81,85,87-88,91-99]	210	180	85.75 (80.24-90.15)
Severe COVID-19 status	30 [46-49,53-57,60-69,72,74,85-86,88,90-91,93-94,96,98]	120	118	98.33 (94.11-99.80)
Mechanical Ventilation	39 [46-48,52,54-68,71,73-77,79-81,84,87,89-91,93-98]	208	201	96.63 (93.19-98.64)
Diabetes	54 [46-99]	248	85	34.27 (28.39-40.54)
Hypertension	54 [46-99]	248	118	47.58 (40.23-53.99)
COPD	53 [46-75,77-99]	247	45	18.21 (13.61-23.61)
Obesity	52 [46-62, 64-84,86-99]	245	48	19.59 (14.81-25.12)
Malignancy	53 [46-84, 86-99]	246	20	8.13 (5.04-12.28)
Steroid therapy	41 [46-63,66,68-69,71-72,75-81,83-84,87-90,92,94,96-98]	203	126	62.06 (55.01-68.77)
Survived	45 [46-58,60-64,66,68-69,71-75,77-84,86,88-96,98-99]	179	71	39.66 (32.44-47.23)
Died	45 [46-58,60-64,66,68-69,71-75,77-84,86,88-96,98-99]	179	108	60.33 (52.77-67.56)

ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease; [references of studies included in proportion analysis]

Among the affected, a very high prevalence of mechanical ventilation (201, 96.6%), ICU admission (180, 85.7%) and use of corticosteroids (126, 62%) was seen. Most (118, 98.3%) patients had severe COVID-19 infection. A mortality of 60.3% (108/179) was seen. When data for those who survived and died due to aspergillosis infection was compared, mechanical ventilation was significantly associated with mortality ($p<0.05$). Besides, other factors like ICU admission, COVID-19 severity, hypertension, and diabetes mellitus were more frequent in patients who died (Table 5). Among the species, *Aspergillus fumigatus* (*A. fumigatus)* was significantly the dominant species in these infections ($p = 0.03$). Antifungal and presumptive antibiotic treatment was more frequent in those who died. However, the use of steroids in COVID-19 at greater than recommended doses was significantly seen in those who succumbed to the infection ($p=0.04$). Aspergillosis infection post-COVID-19 infection (days) was comparable in both groups.

Candidiasis

For infection with *Candida* spp. in COVID-19 patients, 15 studies were eligible, reporting 199 cases.

Table 5: Comparison of epidemiological and clinical characteristics of patients with COVID-19-associated pulmonary aspergillosis (CAPA) (Survived v/s Died)

Parameters	Total	Survived (%)	Died (%)	P value
Subjects	109	37 (33.94)	61 (55.96)	
Not mentioned		*11 (10.28)*		
Demographic data				
Age	98	63.09 ±13.16	63.54 ±13.20	0.71

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Male	76	29 (38.15)	47 (61.84)	0.87
Female	22	8 (36.36)	14 (63.63)	
Risk factor				
ICU admission	80	25 (31.25)	40 (50.00)	1.00
Not mentioned	*18*	*6 (33.33)*	*12 (66.66)*	
Severe COVID-19 status	62	26 (41.93)	33 (53.22)	0.58
Not mentioned	*36*	*9 (25.00)*	*27 (75.00)*	
Mechanical ventilation	89	27 (30.33)	41 (46.06)	**0.00**
Not mentioned	*9*	*9 (100)*	*0*	
Diabetes	98	16 (16.32)	18 (18.36)	0.19
Hypertension		17 (17.34)	30 (30.61)	0.83
COPD		3 (3.06)	12 (12.24)	0.15
Obesity		8 (8.16)	12 (12.24)	0.80
Malignancy		1 (1.02)	6 (6.12)	0.24
Chronic kidney disease		2 (2.02)	3 (3.06)	1.00
Dyslipidaemia		3 (3.06)	7 (7.14)	0.73
Species				
A. fumigatus	59	20 (33.89)	24 (40.67)	**0.03**
A. niger		0	4 (6.77)	0.28
A. flavus		1 (1.69)	2 (3.38)	1.00
A. terreus		0	4 (6.77)	0.28
A. penicillioides		0	1 (1.69)	1.00
A. ochraceus		0	1 (1.69)	1.00
A. lentulus		0	1 (1.69)	1.00
A. proliferans		1 (1.69)	0	0.37
Not mentioned	*39*	*15 (25.42)*	*24 (61.53)*	
Bacterial coinfection	70	5 (7.14)	14 (20.00)	0.17
Not mentioned	*28*	*8 (28.57)*	*20 (71.42)*	
Antibiotic treatment	98	19 (19.38)	30 (30.61)	1.00
Azithromycin		7 (7.14)	11 (11.22)	1.00
Piperacillin-tazobactam		6 (6.12)	8 (8.16)	0.76
Carbapenem		4 (4.08)	13 (13.26)	0.27
3rd generation cephalosporins		6 (6.12)	12 (12.24)	0.79
Antifungal treatment	91	37 (40.65)	50 (54.94)	0.14
Voriconazole		24 (26.37)	40 (43.95)	1.00
Isavuconazole		2 (2.19)	2 (2.19)	0.63
Echinocandin		4 (4.39)	7 (7.69)	1.00
Amphotericin-B		8 (8.79)	9 (9.89)	0.41
Not mentioned	*7*	*0*	*7 (100)*	
Steroid therapy	87	18(20.68)	38 (43.67)	0.25
Not mentioned	*11*	*5 (45.45)*	*6 (54.54)*	
<10 days	35	7(20.00)	16 (45.71)	1.00
>10 days		3 (8.57)	9 (25.71)	1.00
More than the recommended dose		6 (17.14)	23 (65.71)	**0.04**
Not mentioned	*63*	*27 (42.85)*	*36 (57.14)*	
Coinfection	8	4 (50.00)	4 (50.00)	0.71
Average number of days post COVID-19	40	15.79 ±12.40	15.53 ±12.00	1.00
Not mentioned	23	6 (26.08)	17 (73.91)	

ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease

The prevalence summary of epidemiological factors of *Candida* in COVID-19-associated candidiasis (CAC) has been shown in Table 6.

Among these, 185 (92.9%) cases had bloodstream infections (BSI), while 4 (2%) cases had respiratory tract infections.

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Table 6: Prevalence summary of epidemiological factors of *Candida* in COVID-19-associated candidiasis (CAC)

Parameter	Studies (N)	Sample size (N)	Positive cases (n)	Occurrence % (95% CI)
Male	10 [100-105,108,111-112,114]	150	89	59.33 (51.02-67.27)
Female	10 [100-105,108,111-112,114]	150	60	40.00 (32.10-48.31)
ICU admission	14 [100-113]	186	156	83.87 (77.78-88.85)
Severe COVID-19 status	14 [100-112, 114]	183	173	94.53 (90.18-97.35)
Diabetes	15 [100-114]	187	48	25.66 (19.57-32.55)
Hypertension	15 [100-114]	187	73	39.03 (32.00-46.43)
COPD	15 [100-114]	187	26	13.90 (9.29-19.70)
Obesity	15 [100-114]	187	19	10.16 (6.23-15.41)
Malignancy	15 [100-114]	187	17	9.09 (5.39-14.16)
C. albicans	12 [100-104,106-107,109-113]	74	50	67.56 (55.68-78.00)
C. tropicalis	12 [100-104,106-107,109-113]	74	5	6.75 (2.23-15.07)
C. glabrata	12 [100-104,106-107,109-113]	74	6	8.10 (3.03-16.82)
C. parapsilosis	12 [100-104,106-107,109-113]	74	5	6.75 (2.23-15.07)
C. auris	12 [100-104,106-107,109-113]	74	4	5.40 (1.49-13.27)
Steroid therapy	15 [100-114]	187	82	43.85 (36.62-51.20)
Antibiotic treatment	13 [100-104,106,108-114]	163	122	74.84 (67.40-81.30)
Antifungal treatment	15 [100-114]	187	45	24.06 (18.13-30.84)
Azoles	15 [100-114]	187	32	17.11 (12.01-23.29)
Echinocandin	15 [100-114]	187	24	12.83 (8.40-18.49)
Amphotericin-B	15 [100-114]	187	3	1.60 (0.33-4.62)
Survived	9 [100, 102, 104-107, 111-112,114]	56	28	50.00 (36.34-63.66)
Died	9 [100, 102, 104-107, 111-112,114]	56	27	48.21 (34.66-61.97)

ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease; [references of studies included in proportion analysis]

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Two cases reported oral infection, and one case involved urinary tract infection. The major spp. was *C. albicans* (50, 67.5%), followed by *C. glabrata* (5, 8.1%), *C. tropicalis* (5, 6.7%), *C. parapsilosis* (5, 6.7%) and *C. auris* (4, 5.4%).

The majority of the cases had severe COVID-19 infection and had ICU admission (94.5% and 83.8%, respectively). Prior steroid therapy was seen in 43.8% (82/187) cases. Among the different antifungal treatments, azoles (32, 17.1%) followed by echinocandin (24, 12.8%) were the most commonly used agents. The data regarding the duration and dose of steroids and other comorbidities was not available. Patients' data on mechanical ventilation in case of candidiasis infection was also insufficient. Survival was 50% (28/56) in these infected cases.

Pneumocystosis

A total of 7 studies with 16 cases of *Pneumocystis jiroveci* (*P. jirovecî*) infection were reported, among which 3/15 (20%) cases were associated with human immunodeficiency virus (HIV). In contrast, 12/15 (80%) cases were not associated with HIV. Among the cases, the majority (11 cases, 68.7%) survived. Of the 16 cases, 10 (62.5%) cases were incidentally diagnosed using *P. jiroveci*-specific primers in BAL samples of COVID-19 patients.

Histoplasmosis

For histoplasmosis in COVID-19 patients, five studies reported 5 cases comprising three males and two females with a mean age of 34.8 years. None had a history of ICU admission for diabetes mellitus or hypertension. An average of 52.3 days were noted post-COVID-19 in patients with histoplasmosis. Only 2 (40%) patients received prior steroid therapy. Among them, 2 out of 4 (50%) cases were associated with HIV. All the cases were treated with itraconazole with or without amphotericin B, and there was 100% survival.

Trichosporonosis

A study from Brazil reported 5 cases of bloodstream infection with *Trichosporon asahii* (*T. asahii)* in patients with severe COVID-19. Fungal infection in these patients was seen after a mean of 22.4 days post-COVID-19 infection. Of the 5 cases, 4 were males, and the average age was 70.2 years. All were mechanically ventilated in the ICU and had received steroid therapy for an average of 22.2 days. Nearly 80% (4/5) had a fatal course.

Saccharomyces infection

Two studies reported 3 cases of *Saccharomyces* infection with oral lesions in one and BSI in the other two. All three cases were hypertensive males, with one also being diabetic, with a mean age of 72 years. All had been mechanically ventilated and had a history of ICU admission. The BSI was seen post *Saccharomyces* supplementation. The average day for fungal infection post-COVID-19 was 28 days. All were treated with fluconazole with or without anidulafungin; survival was 100%.

Cryptococcosis

This fungus was reported in 2 patients with COVID-19 in 2 studies. Both were 29-year-old males, one with HIV and diagnosed as coinfection with COVID-19, while the other with autoimmune hemolytic anaemia (AIHA) was diagnosed 27 days post-COVID-19. Unfortunately, the second patient died even though both had moderate COVID-19.

Others

Single cases of infection with *Fusarium proliferatum* and *Coccidioides* were reported in 2 different reports in the COVID-19 patients. Fusariosis was seen in a 57-year-old male diabetic, hypertensive and obese case of severe COVID-19 after nine days of COVID-19 diagnosis. Coccidioidomycosis was seen as a coinfection with COVID-19 without any comorbidity but with heart failure. Both patients survived.

DISCUSSION

Diverse fungal infections were seen in association with COVID-19 globally, as evidenced by this systematic review. While aspergillosis and invasive candidiasis have been the most common fungal co infection or superinfection worldwide,[142], the unprecedented emergence of mucormycosis, especially in the Indian context, accounted for the predominance of mucormycosis cases in COVID-19 patients. This review showed that among the published reports, the prevalence of mucormycosis cases was the highest (42.5%), with 278 cases (75.13%) reported from India.

Several factors have been implicated in the increase in fungal coinfection in COVID-19 patients, also noted in the present study. Previous systematic reviews have already hinted towards the excessive use of antibacterial agents without evidence of coinfections. [143, 144] The use of corticosteroids, previously advocated

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for any viral pneumonia, was found to be associated with several secondary fungal infections.[30]

CAM has been reported to have a lower frequency than other COVID-19-associated fungal infections unless reports from India indicate its importance.[142] It was considered a 'notifiable disease' and earned an epidemic status in many states of India.[2, 145] It is evident that CAM was restricted to the Indian subcontinent rather than involving the entire world. The initial period (first wave) of the pandemic in India was also associated with an increase in twice the number of mucormycosis cases as against the pre-COVID-19 period.[5] Two potential factors that public health experts opined had contributed to the full-fledged rise of these cases were the injudicious and excessive usage of corticosteroids, both in the hospitals and the community, in COVID-19 treatment in the 'diabetes capital' of the world.[146] A systematic review of mucormycosis in India revealed uncontrolled hyperglycemia due to the enormous burden of the diabetic population, as well as dysregulation due to COVID-19 infection was one of the critical factors for this infection.[146] The most common species of *Mucor* was not revealed in this study due to a lack of data from most of the studies. However, in the Indian context, *Rhizopus arrhizus* has been reported to be the predominant pathogenic species in CAM.[5] The diagnosis was more difficult owing to the challenges in isolating the fungus and lack of clinical suspicion.[30] Consequently, this study revealed that a significant proportion (71.42%) of those who survived CAM infection presented as coinfection, enabling early diagnosis.

Among other fungal infections, invasive pulmonary aspergillosis (IPA) in COVID-19 patients caused an increased burden of morbidity and mortality.[8] The development of CAPA resulted from interplay between different factors of the epidemiological triad,[6,8] including mechanical ventilation, infection due to *A. fumigatus* spp. and exposure to corticosteroids at higher than the recommended dose, as revealed by this study.

Until mucormycosis emerged, invasive candidiasis was reported as the second most common fungal infection in COVID-19 patients. There has been evidence of a deranged immune response against *C. albicans*, the commonest reported spp., in COVID-19 patients, increasing their susceptibility to invasive candidiasis.[147] Invasive candidiasis accounts for 19-40% of mortality in hospitals, often as high as 70% in ICU.[148] Among the non-albicans species, *C. glabrata* infection was the commonest. However, even *C. auris* infections have been reported in long-term care (LTC) facilities, which might be related to the limited resources required for adequate maintenance of infection control practices.[142]

There have been issues regarding wrong diagnosis and mismanagement of *P. jiroveci* infection during COVID-19 due to similarity in presentation.[149] *Pneumocystis* infection is otherwise commonly associated with immunocompromised patients, particularly with HIV infection.[150] Interestingly, of the reported cases, only 20% cases were in HIV patients. The presence of *P. jiroveci* infections in 80% of the COVID-19-infected patients is indirect evidence of the immune dysregulation caused by the virus.

The major challenge with fungal pneumonia, such as histoplasmosis, blastomycosis, and coccidioidomycosis, is the similarity in the presentation of COVID-19 pneumonia and its timely diagnosis. Previous data had suggested that COVID-19 patients with corticosteroid therapy and HIV infections are commonly associated with histoplasmosis.[1] Incidentally, of the affected patients, 40% had received prior steroid therapy and 50% were associated with HIV.

Trichosporon has been considered a re-emerging fungal pathogen following the excessive use of echinocandins in managing invasive fungal infections.[151,152] Once the second commonest non-*Candida* cause of bloodstream infection due to any fungi in malignancy, this pathogen has shown its propensity for fatal infection in COVID-19 patients.[153] Among 870 cases of fungal infections, a single study reported 5 cases of BSI with *T. asahii* from Brazil.[152] All had a history of ICU admission. The recognized risk factors, like invasive mechanical devices in the form of central venous catheter (CVC) and mechanical ventilation, were present in all the cases. Additionally, exposure to broad-spectrum antibiotics without any evidence of bacterial coinfection initially and exposure to steroid therapy was also present, emphasizing the importance of judicious use of antibiotics, antifungals and steroids. The majority (4/5) also had BSI due to *Candida* spp before or simultaneously with this pathogen. As evident elsewhere, a significant risk factor for invasive *Trichosporon* is unregulated diabetes mellitus or hyperglycaemia, seen in 40% of the cases in the present study.[153]

There have been several reports of possible mechanisms and challenges in immune responses in the form of 'storm' with enormous cytokines release and 'virus-driven hyperinflammation' against the

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SARS-CoV$_2$.[154] Consequently, known pathogens like *Cryptococcus neoformans* have also taken the opportunity to infect the COVID-19 infected susceptible host.

Other less frequently reported fungal infections, like those with *Saccharomyces*, *Fusarium* and *Coccidioides*, were seen in COVID-19 patients with underlying comorbidity conditions and known risk factors. The only positive outcome in these infections was the 100% survival rate.

This review provides a comprehensive overview of 10 different fungal infections reported in COVID-19 patients and their epidemiological factors. However, the article had few limitations. We could not associate all the factors with regard to all the fungal infections due to paucity and lack of uniformity in the data in the reported studies. Additionally, due to a lack of data, both descriptive and observational studies were considered, accounting for substantial data variations. Data on essential factors like biochemical and immunological parameters concerning COVID-19 infection, dose and duration of steroids for all the cases, and use of other therapeutic options like immunosuppressants and immunomodulators could not be analyzed due to insufficiency. The considerable heterogeneity noted for a few of the epidemiological factors could be accounted for by the variations in the number of study subjects reported in each study, as the majority of the selected studies were case reports. Nonetheless, we endeavoured to provide information on the global prevalence of fungal infections in COVID-19 patients and the factors commonly associated with the common infections. Lastly, this comprehensive review brought forward several issues and challenges that could have led to the emergence of these fungal coinfections.

CONCLUSION

Based on published data in major electronic databases, mucormycosis, followed by invasive pulmonary aspergillosis and invasive candidiasis, have been the most prevalent coinfections/superinfections in COVID-19 patients. While in CAM, survival was better in those diagnosed early, in CAPA, mechanical ventilation, a larger dose of corticosteroids than recommended and infection with *A. fumigatus* were significant associations among those who succumbed to the condition. It is essential to provide the best medical practices to tackle these infections. Future studies should suggest innovative strategies to tackle such infections and the pandemic.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

SS: Literature Search; Data Extraction; Data Analysis; Manuscript Writing

AS: Literature Search; Data Extraction

TB: Conceptualization, Supervision; Data Extraction; Review & Editing

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